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<b>(21) International Application Number:</b> PCT/US00/09688 <b>(22) International Filing Date:</b> 10 April 2000 (10.04.00)  <b>(30) Priority Data:</b> 09/288,950 9 April 1999 (09.04.99) US 09/346,327 2 July 1999 (02.07.99) US  <b>(71) Applicant (for all designated States except US):</b> CORIXA CORPORATION [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> REED, Steven, G. [US/US]; 2843 - 122nd Place NE, Bellevue, WA 98005 (US). XU, Jiangchun [US/US]; 15805 SE 43rd Place, Bellevue, WA 98006 (US). DILLON, Davin, C. [US/US]; 21607 NE 24th Street, Redmond, WA 98053 (US).  <b>(74) Agents:</b> POTTER, Jane, E.R.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US) et al.	<b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>	
<b>(54) Title:</b> COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE  <b>(57) Abstract</b>  Compounds and methods for the treatment and diagnosis of breast cancer are provided. The inventive compounds include polypeptides containing at least a portion of a breast tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of breast cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.		

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COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS  
OF BREAST CANCER AND METHODS FOR THEIR USE

5 TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment and diagnosis of breast cancer. The invention is more particularly related to polypeptides comprising at least a portion of a protein that is preferentially expressed in breast tumor tissue and to polynucleotides encoding such polypeptides.

10 Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for treatment of breast cancer. Additionally such polypeptides and polynucleotides may be used in the immunodiagnosis of breast cancer.

BACKGROUND OF THE INVENTION

15 Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast

20 cancer are now one in eight.

No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) and aggressive treatment, which may include one or more of a variety of

25 treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. *See, e.g.,* Porter-Jordan and Lippman, *Breast Cancer* 8:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high

mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for therapy and diagnosis of breast cancer. The present invention fulfills these needs and  
5 further provides other related advantages.

#### SUMMARY OF THE INVENTION

The present invention provides compounds and methods for immunotherapy of breast cancer. In one aspect, isolated polypeptides are provided  
10 comprising at least an immunogenic portion of a breast tumor protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein the breast tumor protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-  
15 97, 102 and 107, (b) complements of said nucleotide sequences and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. In specific embodiments, the isolated polypeptides of the present invention comprise an amino acid sequence of SEQ ID NO: 98, 99 or 101.

In related aspects, isolated polynucleotides encoding the above  
20 polypeptides are provided. In specific embodiments, such polynucleotides comprise sequences provided in SEQ ID NOS: 3, 10, 17, 24, 45-52 and 55-67, 72, 73, 89-97, 102 and 107. The present invention further provides expression vectors comprising the above polynucleotides and host cells transformed or transfected with such expression vectors. In preferred embodiments, the host cells are selected from the  
25 group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known breast antigen.

The present invention also provides pharmaceutical compositions  
30 comprising at least one of the above polypeptides, or a polynucleotide encoding such a polypeptide, and a physiologically acceptable carrier, together with vaccines

comprising at least one or more such polypeptide or polynucleotide in combination with a non-specific immune response enhancer. Pharmaceutical compositions and vaccines comprising one or more of the above fusion proteins are also provided.

In related aspects, pharmaceutical compositions for the treatment of breast cancer comprising at least one polypeptide and a physiologically acceptable carrier are provided, wherein the polypeptide comprises an immunogenic portion of a breast tumor protein or a variant thereof, the breast tumor protein being encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106, (b) complements of said nucleotide sequences, and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. The invention also provides vaccines for the treatment of breast cancer comprising such polypeptides in combination with a non-specific immune response enhancer, together with pharmaceutical compositions and vaccines comprising at least one polynucleotide comprising a sequence provided in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106.

In yet another aspect, methods are provided for inhibiting the development of breast cancer in a patient, comprising administering an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

The present invention also provides methods for immunodiagnosis of breast cancer, together with kits for use in such methods. In one specific aspect of the present invention, methods are provided for detecting breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one

of the above polypeptides; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as  
5 diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of breast cancer.

The present invention further provides methods for detecting breast cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting  
10 the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the  
15 oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

In a further aspect, the present invention provides a method for detecting breast cancer in a patient comprising: (a) obtaining a biological sample  
20 from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group  
25 consisting of SEQ ID NOS: 1-97, 100 and 102-107.

In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein

are hereby incorporated by reference in their entirety as if each was incorporated individually.

5 BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figs. 1A and B show the specific lytic activity of a first and a second B511S-specific CTL clone, respectively, measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares).

- 10 SEQ ID NO: 1 is the determined 3'cDNA sequence of 1T-5120  
SEQ ID NO: 2 is the determined 3'cDNA sequence of 1T-5122  
SEQ ID NO: 3 is the determined 3'cDNA sequence of 1T-5123  
SEQ ID NO: 4 is the determined 3'cDNA sequence of 1T-5125  
SEQ ID NO: 5 is the determined 3'cDNA sequence of 1T-5126  
15 SEQ ID NO: 6 is the determined 3'cDNA sequence of 1T-5127  
SEQ ID NO: 7 is the determined 3'cDNA sequence of 1T-5129  
SEQ ID NO: 8 is the determined 3'cDNA sequence of 1T-5130  
SEQ ID NO: 9 is the determined 3'cDNA sequence of 1T-5133  
SEQ ID NO: 10 is the determined 3'cDNA sequence of 1T-5136  
20 SEQ ID NO: 11 is the determined 3'cDNA sequence of 1T-5137  
SEQ ID NO: 12 is the determined 3'cDNA sequence of 1T-5139  
SEQ ID NO: 13 is the determined 3'cDNA sequence of 1T-5142  
SEQ ID NO: 14 is the determined 3'cDNA sequence of 1T-5143  
SEQ ID NO: 15 is the determined 5'cDNA sequence of 1T-5120  
25 SEQ ID NO: 16 is the determined 5'cDNA sequence of 1T-5122  
SEQ ID NO: 17 is the determined 5'cDNA sequence of 1T-5123  
SEQ ID NO: 18 is the determined 5'cDNA sequence of 1T-5125  
SEQ ID NO: 19 is the determined 5'cDNA sequence of 1T-5126  
SEQ ID NO: 20 is the determined 5'cDNA sequence of 1T-5127  
30 SEQ ID NO: 21 is the determined 5'cDNA sequence of 1T-5129  
SEQ ID NO: 22 is the determined 5'cDNA sequence of 1T-5130

- SEQ ID NO: 23 is the determined 5'cDNA sequence of 1T-5133
- SEQ ID NO: 24 is the determined 5'cDNA sequence of 1T-5136
- SEQ ID NO: 25 is the determined 5'cDNA sequence of 1T-5137
- SEQ ID NO: 26 is the determined 5'cDNA sequence of 1T-5139
- 5 SEQ ID NO: 27 is the determined 5'cDNA sequence of 1T-5142
- SEQ ID NO: 28 is the determined 5'cDNA sequence of 1T-5143
- SEQ ID NO: 29 is the determined 5'cDNA sequence of 1D-4315
- SEQ ID NO: 30 is the determined 5'cDNA sequence of 1D-4311
- SEQ ID NO: 31 is the determined 5'cDNA sequence of 1E-4440
- 10 SEQ ID NO: 32 is the determined 5'cDNA sequence of 1E-4443
- SEQ ID NO: 33 is the determined 5'cDNA sequence of 1D-4321
- SEQ ID NO: 34 is the determined 5'cDNA sequence of 1D-4310
- SEQ ID NO: 35 is the determined 5'cDNA sequence of 1D-4320
- SEQ ID NO: 36 is the determined 5'cDNA sequence of 1E-4448
- 15 SEQ ID NO: 37 is the determined 5'cDNA sequence of 1S-5105
- SEQ ID NO: 38 is the determined 5'cDNA sequence of 1S-5110
- SEQ ID NO: 39 is the determined 5'cDNA sequence of 1S-5111
- SEQ ID NO: 40 is the determined 5'cDNA sequence of 1S-5116
- SEQ ID NO: 41 is the determined 5'cDNA sequence of 1S-5114
- 20 SEQ ID NO: 42 is the determined 5'cDNA sequence of 1S-5115
- SEQ ID NO: 43 is the determined 5'cDNA sequence of 1S-5118
- SEQ ID NO: 44 is the determined 5'cDNA sequence of 1T-5134
- SEQ ID NO: 45 is the determined 5'cDNA sequence of 1E-4441
- SEQ ID NO: 46 is the determined 5'cDNA sequence of 1E-4444
- 25 SEQ ID NO: 47 is the determined 5'cDNA sequence of 1E-4322
- SEQ ID NO: 48 is the determined 5'cDNA sequence of 1S-5103
- SEQ ID NO: 49 is the determined 5'cDNA sequence of 1S-5107
- SEQ ID NO: 50 is the determined 5'cDNA sequence of 1S-5113
- SEQ ID NO: 51 is the determined 5'cDNA sequence of 1S-5117
- 30 SEQ ID NO: 52 is the determined 5'cDNA sequence of 1S-5112

- SEQ ID NO: 53 is the determined cDNA sequence of 1013E11  
SEQ ID NO: 54 is the determined cDNA sequence of 1013H10  
SEQ ID NO: 55 is the determined cDNA sequence of 1017C2  
SEQ ID NO: 56 is the determined cDNA sequence of 1016F8  
5 SEQ ID NO: 57 is the determined cDNA sequence of 1015F5  
SEQ ID NO: 58 is the determined cDNA sequence of 1017A11  
SEQ ID NO: 59 is the determined cDNA sequence of 1013A11  
SEQ ID NO: 60 is the determined cDNA sequence of 1016D8  
SEQ ID NO: 61 is the determined cDNA sequence of 1016D12  
10 SEQ ID NO: 62 is the determined cDNA sequence of 1015E8  
SEQ ID NO: 63 is the determined cDNA sequence of 1015D11  
SEQ ID NO: 64 is the determined cDNA sequence of 1012H8  
SEQ ID NO: 65 is the determined cDNA sequence of 1013C8  
SEQ ID NO: 66 is the determined cDNA sequence of 1014B3  
15 SEQ ID NO: 67 is the determined cDNA sequence of 1015B2  
SEQ ID NO: 68-71 are the determined cDNA sequences of previously identified  
antigens  
SEQ ID NO: 72 is the determined cDNA sequence of JJ9434  
SEQ ID NO: 73 is the determined cDNA sequence of B535S  
20 SEQ ID NO: 74-88 are the determined cDNA sequence of previously identified  
antigens  
SEQ ID NO: 89 is the determined cDNA sequence of B534S  
SEQ ID NO: 90 is the determined cDNA sequence of B538S  
SEQ ID NO: 91 is the determined cDNA sequence of B542S  
25 SEQ ID NO: 92 is the determined cDNA sequence of B543S  
SEQ ID NO: 93 is the determined cDNA sequence of P501S  
SEQ ID NO: 94 is the determined cDNA sequence of B541S  
SEQ ID NO: 95 is an extended cDNA sequence for 1016F8 (also referred to as  
B511S)  
30 SEQ ID NO: 96 is an extended cDNA sequence for 1016D12 (also referred to as

B532S)

SEQ ID NO: 97 is an extended cDNA sequence for 1012H8 (also referred to as B533S)

SEQ ID NO: 98 is the predicted amino acid sequence for B511S

5 SEQ ID NO: 99 is the predicted amino acid sequence for B532S

SEQ ID NO: 100 is the determined full-length cDNA sequence for P501S

SEQ ID NO: 101 is the predicted amino acid sequence for P501S

SEQ ID NO: 102 is the determined cDNA sequence of clone #19605, also referred to as 1017C2, showing no significant homology to any known gene

10 SEQ ID NO: 103 is the determined 3' end cDNA sequence for clone #19599, showing homology to the Tumor Expression Enhanced gene

SEQ ID NO: 104 is the determined 5' end cDNA sequence for clone #19599, showing homology to the Tumor Expression Enhanced gene

15 SEQ ID NO: 105 is the determined cDNA sequence for clone #19607, showing homology to Stromelysin-3

SEQ ID NO: 106 is the determined cDNA sequence for clone #19601, showing homology to Collagen

SEQ ID NO: 107 is the determined cDNA sequence of clone #19606, also referred to as B546S, showing no significant homology to any known gene

20

## DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the immunotherapy and diagnosis of breast cancer. The inventive compositions are generally isolated polypeptides that comprise at least  
25 a portion of a breast tumor protein. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In particular, the subject invention discloses isolated polypeptides comprising at least a portion of a human breast tumor protein, or a variant thereof,  
30 wherein the breast tumor protein includes an amino acid sequence encoded by a

polynucleotide molecule including a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, the complements of said nucleotide sequences, and variants thereof. In certain specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 98, 99 and 101, and variants thereof. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above breast proteins may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may be immunoreactive and/or antigenic.

As used herein, an "immunogenic portion" of a human breast tumor protein is a portion that is capable of eliciting an immune response in a patient inflicted with breast cancer and as such binds to antibodies present within sera from a breast cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of breast cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known

in the art and include those summarized in Paul, *Fundamental Immunology*, 3<sup>rd</sup> ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides. A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the therapeutic, antigenic and/or immunogenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the

following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA*, 2:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within

the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be “identical” if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A “comparison window” as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, more preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad. Sci. USA* 80:726-730.

Preferably, the “percentage of sequence identity” is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Also included in the scope of the present invention are alleles of the genes encoding the nucleotide sequences recited herein. As used herein, an “allele” or “allelic sequence” is an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given gene may have none, one, or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone or in combination with the others, one or more times in a given sequence.

For breast tumor polypeptides with immunoreactive properties, variants may alternatively be identified by modifying the amino acid sequence of one of the above polypeptides, and evaluating the immunoreactivity of the modified polypeptide. For breast tumor polypeptides useful for the generation of diagnostic binding agents, a variant may be identified by evaluating a modified polypeptide for the ability to generate antibodies that detect the presence or absence of breast cancer. Such modified sequences may be prepared and tested using, for example, the representative procedures described herein.

The breast tumor proteins of the present invention, and polynucleotide molecules encoding such proteins, may be isolated from breast tumor tissue using any

of a variety of methods well known in the art. Polynucleotide sequences corresponding to a gene (or a portion thereof) encoding one of the inventive breast tumor proteins may be isolated from a breast tumor cDNA library using a subtraction technique as described in detail below. Examples of such DNA sequences are provided in SEQ ID NOS: 1- 97, 100 and 102-107. Partial polynucleotide sequences thus obtained may be used to design oligonucleotide primers for the amplification of full-length polynucleotide sequences in a polymerase chain reaction (PCR), using techniques well known in the art (see, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989). Once a polynucleotide sequence encoding a polypeptide is obtained, any of the above modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA*, 2:183, 1983).

The breast tumor polypeptides disclosed herein may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Alternatively, any of the above polypeptides may be produced recombinantly by inserting a polynucleotide sequence that encodes the polypeptide into an expression vector and expressing the protein in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an

expression vector containing a polynucleotide molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as CHO cells. The polynucleotide sequences expressed in this manner may  
5 encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary  
10 sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

15 In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known breast tumor antigen, together with variants of such fusion proteins.

A polynucleotide sequence encoding a fusion protein of the present  
20 invention is constructed using known recombinant DNA techniques to assemble separate polynucleotide sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a polynucleotide sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a polynucleotide sequence encoding the second polypeptide so that the reading frames  
25 of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds  
30 into its secondary and tertiary structures. Such a peptide linker sequence is

incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated polynucleotide sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of polynucleotides are located only 5' to the polynucleotide sequence encoding the first polypeptide. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the polynucleotide sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91 (1997)).

Polypeptides of the present invention that comprise an immunogenic portion of a breast tumor protein may generally be used for immunotherapy of breast cancer, wherein the polypeptide stimulates the patient's own immune response to breast tumor cells. In further aspects, the present invention provides methods for using one or more of the immunoreactive polypeptides encoded by a polynucleotide

molecule having a sequence provided in SEQ ID NOS: 1- 97, 100 and 102-107 (or fusion proteins comprising one or more such polypeptides and/or polynucleotides encoding such polypeptides) for immunotherapy of breast cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease. Accordingly, the above immunoreactive polypeptides (or fusion proteins or polynucleotide molecules encoding such polypeptides) may be used to treat breast cancer or to inhibit the development of breast cancer. In a preferred embodiment, the polypeptides are administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the polypeptide or fusion protein is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more of such polypeptides and a non-specific immune response enhancer, wherein the non-specific immune response enhancer is capable of eliciting or enhancing an immune response to an exogenous antigen. Examples of non-specific-immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of breast tumor antigens, either incorporated into a combination polypeptide (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain polynucleotides encoding one or more of the above polypeptides, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems

contain the necessary polynucleotide sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a breast tumor cell antigen on its cell surface. In a preferred embodiment, the polynucleotide molecules may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *PNAS* 91:215-219, 1994; Kass-Eisler et al., *PNAS* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating polynucleotides into such expression systems are well known to those of ordinary skill in the art.

The polynucleotides may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science* 259:1745-1749, 1993, reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked polynucleotides may be increased by coating the polynucleotides onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or polynucleotide that is

effective to raise an immune response (cellular and/or humoral) against breast tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the polynucleotide in a dose) ranges from about 1 pg to about 5 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 µg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of 10 carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium 15 carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of non-specific immune response enhancers may be 20 employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's 25 Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active 30 immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host

immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

In passive immunotherapy, treatment involves the delivery of biologic  
5 reagents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, gamma/delta T lymphocytes, tumor-infiltrating lymphocytes), killer cells (such as  
10 Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for  
15 adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. These *in vitro* culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above,  
20 the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B-cells, may be pulsed with immunoreactive polypeptides or polynucleotide sequence(s) may be introduced into antigen presenting  
25 cells, using standard techniques well known in the art. For example, antigen presenting cells may be transfected or transduced with a polynucleotide sequence, wherein said sequence contains a promoter region appropriate for inducing expression, and can be expressed as part of a recombinant virus or other expression system. Several viral vectors may be used to transduce an antigen presenting cell,  
30 including pox virus, vaccinia virus, and adenovirus. Antigen presenting cells may be

transfected with polynucleotide sequences disclosed herein by a variety of means, including gene-gun technology, lipid-mediated delivery, electroporation, osmotic shock, and particulate delivery mechanisms, resulting in efficient and acceptable expression levels as determined by one of ordinary skill in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term *in vivo*. Studies have demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever, M., et al, "Therapy With Cultured T Cells: Principles Revisited," *Immunological Reviews*, 157:177, 1997).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. (*Crit. Rev. Oncol. Hematol.*, 22(3), 213, 1996). Cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system. The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

In other embodiments, T-cell and/or antibody receptors specific for the polypeptides can be cloned, expanded, and transferred into other vectors or effector

cells for use in adoptive immunotherapy. In particular, T cells may be transfected with the appropriate genes to express the variable domains from tumor specific monoclonal antibodies as the extracellular recognition elements and joined to the T cell receptor signaling chains, resulting in T cell activation, specific lysis, and cytokine release. This enables the T cell to redirect its specificity in an MHC-independent manner. See for example, Eshhar, Z., *Cancer Immunol Immunother*, 45(3-4):131-6, 1997 and Hwu, P., et al, *Cancer Res*, 55(15):3369-73, 1995. Another embodiment may include the transfection of tumor antigen specific alpha and beta T cell receptor chains into alternate T cells, as in Cole, DJ, et al, *Cancer Res*, 55(4):748-52, 1995.

In further embodiments, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al. (*Immunological Reviews*, 157:177, 1997).

Additionally, vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

In one specific embodiment, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

Polypeptides of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human breast tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without breast cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a breast tumor protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic breast cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic breast cancer. Suitable portions of such breast tumor proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic breast cancer in substantially all (*i.e.*, at least about 80%, and preferably at least about 90%) of the patients for which breast cancer would be indicated using the full length protein, and that indicate the absence of breast cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human breast tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human breast tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic breast cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic breast tumors by such procedures are

considered to be useful in assays for detecting primary or metastatic human breast tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human breast  
5 tumors may be used as markers for diagnosing breast cancer or for monitoring disease progression in patients. In one embodiment, breast cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera and urine.

10 The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in  
15 solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by  
20 the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about  $10^3$  L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding  
25 agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by  
30 other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as

polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally  
5 be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by  
10 condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the  
15 sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a  
20 method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The  
25 immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast  
30 cancer. Preferably, the contact time is sufficient to achieve a level of binding that is

at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about  
5 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase),  
10 substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound  
15 polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or  
20 autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time),  
25 followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the  
30 immobilized antibody is incubated with samples from patients without breast cancer.

In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for breast cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this  
5      embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest  
10     area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this  
15     method is considered positive for breast cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled  
20     antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing  
25     second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of breast cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected  
30     to generate a visually discernible pattern when the biological sample contains a level

of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1  $\mu$ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of breast cancer. In this embodiment, assays as described above for the diagnosis of breast cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, breast cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, breast cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may

then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate breast tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides,

differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include  $^{90}\text{Y}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{211}\text{At}$ , and  $^{212}\text{Bi}$ . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, 5 diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a 10 substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an 15 antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on 20 agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino 25 groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a 30 linker group which is cleavable during or upon internalization into a cell. A number

of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous,

intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

5                 Diagnostic reagents of the present invention may also comprise at least a portion of a polynucleotide disclosed herein. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify breast tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide  
10         encoding a breast tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a breast tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a  
15         biological sample.

               As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question, or an oligonucleotide sequence that is anti-sense to a  
20         sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10  
25         contiguous nucleotides of a polynucleotide disclosed herein or that is anti-sense to a polynucleotide sequence disclosed herein. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide that encodes one of the polypeptides disclosed herein or that is anti-sense to a sequence that encodes one of the polypeptides  
30         disclosed herein. Techniques for both PCR based assays and hybridization assays are

well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect breast tumor-specific sequences in biological samples, including blood, urine and/or breast tumor tissue.

The following Examples are offered by way of illustration and not by  
5 way of limitation.

## EXAMPLES

### Example 1

#### 10 ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES

This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

15 A human breast tumor cDNA expression library was constructed from a pool of breast tumor poly A<sup>+</sup> RNA from three patients using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, breast tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total  
20 RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BstX I  
25 adaptors (Invitrogen, Carlsbad, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA 94303), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen, Carlsbad, CA) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human breast cDNA expression library was prepared from a pool of four normal breast tissue specimens. The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The breast tumor library contained  $1.14 \times 10^7$  independent colonies, with more than 90% of clones having a visible insert and the average insert size being 936 base pairs. The normal breast cDNA library contained  $6 \times 10^6$  independent colonies, with 83% of clones having inserts and the average insert size being 1015 base pairs. Sequencing analysis showed both libraries to contain good complex cDNA clones that were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination sequencing.

cDNA library subtraction was performed using the above breast tumor and normal breast cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a breast tumor-specific subtracted cDNA library was generated as follows. Normal breast cDNA library (70  $\mu$ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100  $\mu$ l of H<sub>2</sub>O, heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA), the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10  $\mu$ g breast tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5  $\mu$ l H<sub>2</sub>O. Tracer DNA was mixed with 15  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and

incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12  $\mu$ l H<sub>2</sub>O, mixed with 8  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer, and  
5 subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a breast tumor specific subtracted cDNA library.

10 To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted breast tumor specific library and characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Thirty-eight distinct cDNA clones were found in the subtracted breast tumor-specific cDNA  
15 library. The determined 3' cDNA sequences for 14 of these clones are provided in SEQ ID NO: 1-14, with the corresponding 5' cDNA sequences being provided in SEQ ID NO: 15-28, respectively. The determined one strand (5' or 3') cDNA sequences for the remaining clones are provided in SEQ ID NO: 29-52. Comparison of these cDNA sequences with known sequences in the gene bank using the EMBL  
20 and GenBank databases (Release 97) revealed no significant homologies to the sequences provided in SEQ ID NO: 3, 10, 17, 24 and 45-52. The sequences provided in SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-41, 43 and 44 were found to show at least some degree of homology to known human genes. The sequence of SEQ ID NO: 42 was found to show some homology to a known yeast gene.

25 cDNA clones isolated in the breast subtraction described above were colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Fremont, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array.  
30 mRNA was extracted from the tissue sample to be tested, reverse transcribed, and

fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity.

Data was analyzed using GEMTOOLS Software. Twenty one distinct  
5 cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested. The determined partial cDNA sequences for these clones are provided in SEQ ID NO: 53-73. Comparison of the sequences of SEQ ID NO: 53, 54 and 68-71 with those in the gene bank as described above, revealed some homology to previously identified human genes. No significant homologies were  
10 found to the sequences of SEQ ID NO: 55-67, 72 (referred to as JJ 9434) and 73 (referred to as B535S). In further studies, full length cDNA sequences were obtained for the clones 1016F8 (SEQ ID NO: 56; also referred to as B511S) and 1016D12 (SEQ ID NO: 61; also referred to as B532S), and an extended cDNA sequence was obtained for 1012H8 (SEQ ID NO: 64; also referred to as B533S). These cDNA  
15 sequences are provided in SEQ ID NO: 95-97, respectively, with the corresponding predicted amino acid sequences for B511S and B532S being provided in SEQ ID NO: 98 and 99, respectively.

Analysis of the expression of B511S in breast tumor tissues and in a variety of normal tissues (skin, PBMC, intestine, breast, stomach, liver, kidney, fetal  
20 tissue, adrenal gland, salivary gland, spinal cord, large intestine, small intestine, bone marrow, brain, heart, colon and pancreas) by microarray, northern analysis and real time PCR, demonstrated that B511S is over-expressed in breast tumors, and normal breast, skin and salivary gland, with expression being low or undetectable in all other tissues tested.

25 Analysis of the expression of B532S in breast tumor tissue and in a variety of normal tissues (breast, PBMC, esophagus, HMEC, spinal cord, bone, thymus, brain, bladder, colon, liver, lung, skin, small intestine, stomach, skeletal muscle, pancreas, aorta, heart, spleen, kidney, salivary gland, bone marrow and adrenal gland) by microarray, Northern analysis and real time PCR, demonstrated that

B532S is over-expressed in 20-30% of breast tumors with expression being low or undetectable in all other tissues tested.

In a further experiment, cDNA fragments were obtained from two subtraction libraries derived by conventional subtraction, as described above and  
5 analyzed by DNA microarray. In one instance the tester was derived from primary breast tumors, referred to as Breast Subtraction 2, or BS2. In the second instance, a metastatic breast tumor was employed as the tester, referred to as Breast Subtraction 3, or BS3. Drivers consisted of normal breast.

cDNA fragments from these two libraries were submitted as templates  
10 for DNA microarray analysis, as described above. DNA chips were analyzed by hybridizing with fluorescent probes derived from mRNA from both tumor and normal tissues. Analysis of the data was accomplished by creating three groups from the sets of probes, referred to as breast tumor/mets, normal non-breast tissues, and metastatic breast tumors. Two comparisons were performed using the modified Gemtools  
15 analysis. The first comparison was to identify templates with elevated expression in breast tumors. The second was to identify templates not recovered in the first comparison that yielded elevated expression in metastatic breast tumors. An arbitrary level of increased expression (mean of tumor expression versus the mean of normal tissue expression) was set at approximately 2.2.

20 In the first round of comparison to identify over-expression in breast tumors, two novel gene sequences were identified, hereinafter referred to as B534S and B538S (SEQ ID NO: 89 and 90, respectively), together with six sequences that showed some degree of homology to previously identified genes (SEQ ID NO: 74-79). The sequences of SEQ ID NO: 75 and 76 were subsequently determined to be  
25 portions of B535S (SEQ ID NO: 73). In a second comparison to identify elevated expression in metastatic breast tumors, five novel sequences were identified, hereinafter referred to as B535S, B542S, B543S, P501S and B541S (SEQ ID NO: 73 and 91-94, respectively), as well as nine gene sequences that showed some homology to known genes (SEQ ID NO: 80-88). Clone B534S and B538S (SEQ ID NO: 89 and

90) were shown to be over-expressed in both breast tumors and metastatic breast tumors.

In a subsequent series of studies, 457 clones from Breast Subtraction 2 were analyzed by microarray on Breast Chip 3. As described above, a first comparison to identify over-expression in breast tumors over normal non-breast tissues was performed. This analysis yielded six cDNA clones that demonstrated elevated expression in breast tumor over normal non-breast tissues. Two of these clones, referred to as 1017C2 (SEQ ID NO: 102) and B546S (SEQ ID NO: 107) do not share significant homology to any known genes. Clone B511S also showed over-expression in breast tumor, which was previously described as 1016F8, with the determined cDNA sequence provided in SEQ ID NO: 95 and the predicted amino acid sequence provided in SEQ ID NO: 98. The remaining four clones over-expressed in breast tumor were found to share some degree of homology to Tumor Expression Enhanced Gene (SEQ ID NO: 103 and 104) Stromelysin-3 (SEQ ID NO: 105) or Collagen (SEQ ID NO: 106).

In the second comparison to determine genes with elevated expression in metastatic breast tumors over non-breast normal tissues, a profile similar to the first comparison was derived. The two putatively novel clones, 1017C2 and B546S, SEQ ID NO: 102 and 107, respectively, were overexpressed in metastatic breast tumors. In addition, Tumor Expression Enhanced Gene and B511S also showed elevated expression in metastatic breast tumors.

As described in U.S. Patent Application No. 08/806,099, filed February 25, 1997, the antigen P501S was isolated by subtracting a prostate tumor cDNA library with a normal pancreas cDNA library and with three genes found to be abundant in a previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. The determined full-length cDNA sequence for P501S is provided in SEQ ID NO: 100, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 101. Expression of P501S in breast tumor was examined by microarray analysis. Over-expression was found in prostate tumor, breast tumor

and metastatic breast tumor, with negligible to low expression being seen in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

5

### Example 2

#### GENERATION OF HUMAN CD8+ CYTOTOXIC T-CELLS THAT RECOGNIZE ANTIGEN PRESENTING CELLS EXPRESSING BREAST TUMOR ANTIGENS

10 This Example illustrates the generation of T cells that recognize target cells expressing the antigen B511S, also known as 1016-F8 (SEQ ID NO: 56). Human CD8+ T cells were primed *in-vitro* to the B511S gene product using dendritic cells infected with a recombinant vaccinia virus engineered to express B511S as follows (also see Yee et al., Journal of Immunology (1996) 157 (9):4079-86).

15 Dendritic cells (DC) were generated from peripheral blood derived monocytes by differentiation for 5 days in the presence of 50  $\mu\text{g/ml}$  GMCSF and 30  $\mu\text{g/ml}$  IL-4. DC were harvested, plated in wells of a 24-well plate at a density of  $2 \times 10^5$  cells/well and infected for 12 hours with B511S expressing vaccinia at a multiplicity of infection of 5. DC were then matured overnight by the addition of 3  $\mu\text{g/ml}$  CD40-

20 Ligand and UV irradiated at 100 $\mu\text{W}$  for 10 minutes. CD8+ T cells were isolated using magnetic beads, and priming cultures were initiated in individual wells (typically in 24 wells of a 24-well plate) using  $7 \times 10^5$  CD8+ T cells and  $1 \times 10^6$  irradiated CD8-depleted PBMC. IL-7 at 10 ng/ml was added to cultures at day 1. Cultures were re-stimulated every 7-10 days using autologous primary fibroblasts

25 retrovirally transduced with B511S and the costimulatory molecule B7.1. Cultures were supplemented at day 1 with 15 I.U. of IL-2. Following 4 such stimulation cycles, CD8+ cultures were tested for their ability to specifically recognize autologous fibroblasts transduced with B511S using an interferon- $\gamma$  Elispot assay (see Lalvani et al J. Experimental Medicine (1997) 186:859-965). Briefly, T cells from

30 individual microcultures were added to 96-well Elispot plates that contained autologous fibroblasts transduced to express either B511S or as a negative control

antigen EGFP, and incubated overnight at 37° C; wells also contained IL-12 at 10 ng/ml. Cultures were identified that specifically produced interferon- $\gamma$  only in response to B511S transduced fibroblasts; such lines were further expanded and also cloned by limiting dilution on autologous B-LCL retrovirally transduced with B511S.

- 5 Lines and clones were identified that could specifically recognize autologous B-LCL transduced with B511S but not autologous B-LCL transduced with the control antigens EGFP or HLA-A3. An example demonstrating the ability of human CTL cell lines derived from such experiments to specifically recognize and lyse B511S expressing targets is presented in Figure 1.

10

### Example 3

#### SYNTHESIS OF POLYPEPTIDES

- Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using
- 20 the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60%
- 25 acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

## CLAIMS

1. An isolated polypeptide comprising an immunogenic portion of a breast protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.
2. The isolated polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 98,99 and 101.
3. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of any one of claims 1 and 2.
4. An isolated polynucleotide comprising a sequence provided in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107.
5. An expression vector comprising a polynucleotide according to any one of claims 3 and 4.
6. A host cell transformed with the expression vector of claim 5.
7. The host cell of claim 6 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.
8. A pharmaceutical composition comprising the polypeptide of claim 1 and a physiologically acceptable carrier.
9. A vaccine comprising the polypeptide of claim 1 and a non-specific immune response enhancer.

10. The vaccine of claim 9 wherein the non-specific immune response enhancer is an adjuvant.

11. A vaccine comprising an isolated polynucleotide of any one of claims 3 and 4, and a non-specific immune response enhancer.

12. The vaccine of claim 11 wherein the non-specific immune response enhancer is an adjuvant.

13. A pharmaceutical composition for the treatment of breast cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

14. A vaccine for the treatment of breast cancer comprising a polypeptide and a non-specific immune response enhancer, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

15. The vaccine of claim 14 wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine for the treatment of breast cancer comprising a polynucleotide and a non-specific immune response enhancer, the polynucleotide

comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

17. The vaccine of claim 16, wherein the non-specific immune response enhancer is an adjuvant.

18. A pharmaceutical composition according to any one of claims 8 and 13, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

19. A vaccine according to any one of claims 9, 11, 14 or 16, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

20. A fusion protein comprising at least one polypeptide according to claim 1.

21. A pharmaceutical composition comprising a fusion protein according to claim 20 and a physiologically acceptable carrier.

22. A vaccine comprising a fusion protein according to claim 20 and a non-specific immune response enhancer.

23. The vaccine of claim 22 wherein the non-specific immune response enhancer is an adjuvant.

24. A pharmaceutical composition according to claim 21, for use in manufacture of a medicament for inhibiting the development of breast cancer in a patient.

25. A vaccine according to claim 22, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

26. A method for detecting breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting breast cancer in the patient.

27. The method of claim 26 wherein the binding agent is a monoclonal antibody.

28. The method of claim 27 wherein the binding agent is a polyclonal antibody.

29. A method for monitoring the progression of breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and  
(d) comparing the amount of polypeptide detected in steps (b) and (c)  
to monitor the progression of breast cancer in the patient.

30. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a breast protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

31. A monoclonal antibody according to claim 30, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

32. The monoclonal antibody of claim 31 wherein the monoclonal antibody is conjugated to a therapeutic agent.

33. A method for detecting breast cancer in a patient comprising:  
(a) contacting a biological sample from a patient with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and  
(b) detecting in the sample a polynucleotide sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting breast cancer.

34. The method of claim 33, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NOS: 1-97, 100 and 102-107.

35. A diagnostic kit comprising:

- (a) one or more monoclonal antibodies of claim 30; and
- (b) a detection reagent.

36. A diagnostic kit comprising:

- (a) one or more monoclonal antibodies that bind to a polypeptide encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106, complements of said sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 or 103-106 under moderately stringent conditions; and
- (b) a detection reagent.

37. The kit of claims 35 or 36 wherein the monoclonal antibodies are immobilized on a solid support.

38. The kit of claim 37 wherein the solid support comprises nitrocellulose, latex or a plastic material.

39. The kit of claims 35 or 36 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

40. The kit of claim 39 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

41. The kit of claim 39 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

42. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107 complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions.

43. A diagnostic kit of claim 42 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NOS: 1-97, 100 and 102-107.

44. A method for detecting breast cancer in a patient, comprising:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and
- (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe, thereby detecting breast cancer in the patient.

45. The method of claim 44 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

46. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions.

47. The diagnostic kit of claim 46, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

48. A method for treating breast cancer in a patient, comprising the steps of:

- (a) obtaining peripheral blood cells from the patient;
- (b) incubating the cells in the presence of at least one polypeptide of any one of claims 1 and 2, such that T cells proliferate; and administering the proliferated T cells to the patient.

49. A method for treating breast cancer in a patient, comprising the steps of:

- (a) obtaining peripheral blood cells from the patient;
- (b) incubating the cells in the presence of at least one polynucleotide of any one of claims 3 and 4, such that T cells proliferate; and
- (c) administering the proliferated T cells to the patient.

50. The method of any one of claims 48 and 49 wherein the step of incubating the cells is repeated one or more times.

51. The method of any one of claims 48 and 49 wherein step (a) further comprises separating the T cells from the peripheral blood cells and the cells incubated in step (b) are the T cells.

52. The method of any one of claims 48 and 49 wherein step (a) further comprises separating CD4<sup>+</sup> cells or CD8<sup>+</sup> cells from the peripheral blood cells and the cells proliferated in step (b) are CD4<sup>+</sup> or CD8<sup>+</sup> T cells.

53. The method of any one of claims 48 and 49 wherein step (b) further comprises cloning at least one T cell that proliferated in the presence of the polypeptide.

54. A composition for the treatment of breast cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of any one of claims 1 and 2, in combination with a pharmaceutically acceptable carrier.

55. A composition for the treatment of breast cancer in a patient comprising T cells proliferated in the presence of a polynucleotide of any one of claims 3 and 4, in combination with a pharmaceutically acceptable carrier.

56. A method for treating breast cancer in a patient, comprising the steps of:

- (a) incubating antigen presenting cells in the presence of at least one polypeptide of any one of claims 1 and 2; and
- (b) administering to the patient the incubated antigen presenting cells.

57. A method for treating breast cancer in a patient, comprising the steps of:

- (a) incubating antigen presenting cells in the presence of at least one polynucleotide of any one of claims 3 and 4; and
- (b) administering to the patient the incubated antigen presenting

cells.

58. The method of claims 56 or 57 wherein the antigen presenting cells are selected from the group consisting of dendritic cells, macrophage cells, monocyte cells, fibroblast cells, B-cells or combinations thereof.

59. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of any one of claims 1 and 2, in combination with a pharmaceutically acceptable carrier.

60. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of any one of claims 3 and 4, in combination with a pharmaceutically acceptable carrier.

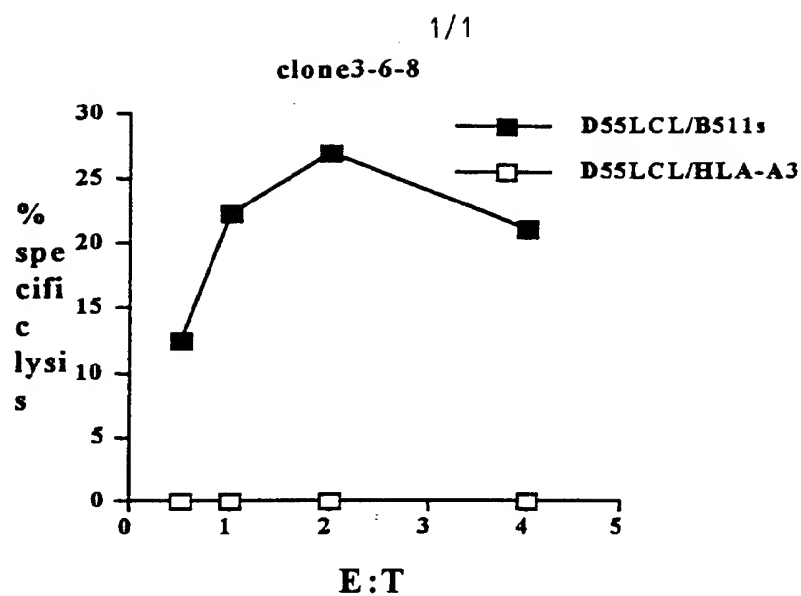


FIGURE 1A

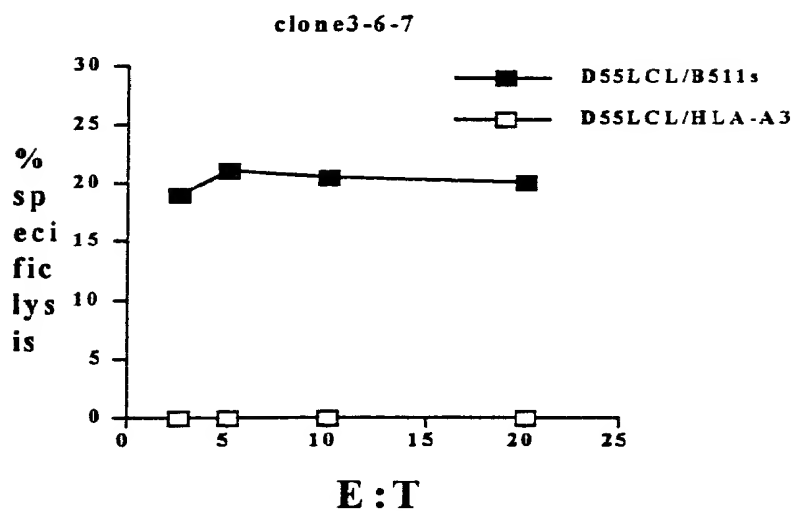


FIGURE 1B

**Figure 1:** Specific lytic activity of B511s-specific CTL clones 3-6-8 and 3-6-7 measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares). Each data point is the average of triplicate measurements.

## SEQUENCE LISTING

<110> Corixa Corporation  
 Reed, Steven G.  
 Xu, Jiangchun  
 Dillon, Davin C.

<120> COMPOUNDS FOR IMMUNOTHERAPY AND  
 DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

<130> 210121.44602PC

<140> PCT

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cctccnaata aaaatnccng gccctactgg gttaagcaac attgcatntc taaagaaacc      300
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 <223> n = A,T,C or G

<400> 19  
 aagggatgca nataatgctg tgtatgagct tgatggaaaa gaactctgta gtgaaaggggt 60  
 tactattgaa catgctnngg ctcggtcacg aggtggaaga ggtagaggac gatactctga 120  
 ccgttttagt agtcgcagac ctcgaaatga tagacgaaat gctccacctg taagaacaga 180  
 anatcgtctt atagttgaga atttatcctc aagagtcagc tggcagggtt gttganatac 240  
 agttttgagt tnttttgatg tggcttttta aaaaagttat gggttactna tggttatattg 300  
 ttttattaaa agtagttttt aattaatgga tntgatggaa ttgttgtttt 350

<210> 20  
 <211> 367

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(367)  
 <223> n = A,T,C or G

<400> 20  
 gntnnnnenca agatcctnct ntccccengg gongccccnc cncngtnat naccggtttn 60  
 ntaanatcnn gccgcncceg aagtctcnc nntgcgcaga tgncccttat ncnennatgn 120  
 ncaattntga cctnnggcga anaatggcng nngtgtatca gtntccnctc tgnngnctct 180  
 tagnatctga ccaactangac cncctatcct ctcaaaccct gtanncngcc ctaatttgtg 240  
 ccaattagt catgntanag cntcctggcc cagatggcct ccatatcctg gtncggcttc 300  
 cgccectacc angncatcen catctactag agcttatccg ctncntgngg cgcaccggnt 360  
 ccccnct 367

<210> 21  
 <211> 366  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(366)  
 <223> n = A,T,C or G

<400> 21  
 cccaacacaa tggctctaagt anaactgtat tgctctgtag tatagttcca cattggcaac 60  
 ctacaatggg aaaatccata cataagtcag ttacttccn atgagcttcc tctttctgaa 120  
 tcttttatct tctgaagaaa gtacacacct tggtnatgat atctttgaat tgcccttctt 180  
 tccaggcatc agttggatga ttcctcatgg taattatggc attatcatat tcttcatact 240  
 tgtcatatga aaacaccagt tctgcccna gatgagcttg ttctgcagct cttagcacct 300  
 tgggaatatt cactctagac cagaaacagc tcccgggtgct ccttcatttt ctgaggctta 360  
 aatttn 366

<210> 22  
 <211> 315  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(315)  
 <223> n = A,T,C or G

<400> 22  
 acttaatgca atctctggag gataatttgg atcaagaaat aaagaanaaa tgaattagga 60  
 gaagaaatna ctgggtnata tttcaatatt ttagaacttt aanaatgttg actatgattt 120  
 caatatattt gtnaaaactg agatacangt ttgacctata tctgcatttt gataattaa 180  
 cnaatnnatt ctatttnaat gttgtttcag agtcacagca cagactgaaa ctttttttga 240  
 atacctnaat atcacacttn tnccttnaat gatgttgaa acaatgatga catgccttna 300  
 gcatataatg tcgac 315

<210> 23

<211> 202  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(202)  
 <223> n = A,T,C or G

<400> 23  
 actaatccag tgtggtgnaa ttccattgtg ttgggcaact caggatatta aatttatnat 60  
 ttaaaaattc ccaagagaaa naaactccag gccctgattg ttccactggg gaattttacc 120  
 aaatgttnca nnaaganatg acgctgattc tgnnaaatct ttttcagaag atagaggaga 180  
 acaccaccg ntccatttta tg 202

<210> 24  
 <211> 365  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(365)  
 <223> n = A,T,C or G

<400> 24  
 ggattttcttg cctttttctc cctttttaag tatcaatgta tgaaatccac ctgtaccacc 60  
 ctttctgcca tacaaccgct accacatctg gctcctagaa cctgttttgc ttccatagat 120  
 ggatctctgga accnagtgtt nacttcattt ttaaacccca ttttagcaga tngtttgctn 180  
 tgggtctgtct gtattcacca tggggcctgt acacaccacg tgtggttata gtcaaacaca 240  
 gtgccctcca ttgtggccac atgggagacc catnaccna tactgcatcc tgggctgatn 300  
 acggcactgc atctnaccg acntgggatt gaacccgggg tgggcagcng aattgaacag 360  
 gatca 365

<210> 25  
 <211> 359  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(359)  
 <223> n = A,T,C or G

<400> 25  
 gtttcctgct tcaacagtgc ttggacggaa cccggcgctc gttccccacc ccggccggcc 60  
 gcccatagcc agccctccgt cacctcttca ccgcaccctc ggactgcccc aaggcccccg 120  
 ccgcncctcc ngcgcncgc agccaccgcc gccncncna cctctccttn gtcccgccnt 180  
 nacaacgcgt ccacctcgca ngttcgccng aactaccacc nggactcata ngccgcccctc 240  
 aaccgcccga tcaacctgga gctctncccc ccgacnttaa cctttccntg tcttacttac 300  
 nttaaccgcc gnttattttg cttnaaaaga acttttcccc aatactttct ttcaccnnt 359

<210> 26  
 <211> 400  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(400)

<223> n = A,T,C or G

<400> 26

agtgaacag	tatatgtgaa	aaggagtttg	tgannagcta	cataaaaata	ttagatatct	60
ttataatttc	caataggata	ctcatcagtt	ttgaataana	gacatattct	agagaaacca	120
ggtttctggt	ttcagatttg	aactctcaag	agcttggaag	ttatcactcc	catcctcacg	180
acnacnaana	aatctnaacn	aacngaana	caatgacttt	tcttagatct	gtcaaagaac	240
ttcagccacg	aggaaaacta	tcnccctnaa	tactggggac	tggaaagaga	gggtacagag	300
aatcacagt	aatcatagcc	caagatcagc	ttgcccggag	ctnaagctng	tacgatnatt	360
acttacaggg	accacttcac	agtnngtnga	tnaantgcon			400

<210> 27

<211> 366

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(366)

<223> n = A,T,C or G

<400> 27

gaatttctta	gaaactgaag	tttactctgt	tccaagatat	atcttcaactg	tcttaaatcaa	60
agggcgctng	aatcatagca	aatattctca	tctttcaact	aactttaagt	agttntcctg	120
gaattttaca	ttttccagaa	aacactcctt	tctgtatctg	tgaagaaag	tgtgcctcag	180
gctgtagact	gggctgcact	ggacacctgc	gggggactct	ggctnagtgn	ggacatggtc	240
agtattgatt	ttctctanac	tcagcctgtg	tagctntgaa	agcatggaac	agattacact	300
gcagttnacg	tcatcccaca	catcttggac	tccnagaccc	ggggagggtca	catagtcctg	360
tatgna						366

<210> 28

<211> 402

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(402)

<223> n = A,T,C or G

<400> 28

agtgggagcc	tcctccttcc	ccactcagtt	ctttacatcc	ccgaggcgca	gctgggcnaa	60
ggaagtggcc	agctgcagcg	cctcctgcag	gcagccaacg	ttcttgctg	tggcctgtgc	120
agacacatcc	ttgccaccac	ctttaccgtc	catcangcct	gacacctgct	gcacccactc	180
gctngctttt	aagccccgat	nggctgcatt	ctgggggact	tgacacaggc	ncgtgatctt	240
gccagcctca	ttgtccaccg	tgaagagcat	ggcaaaaagt	ctgagggggag	tgcattctga	300
anagcttcaa	ggcttcattc	agggccttng	ctnaggcgcc	nctctccatc	tccnggaata	360
acnagaggct	ggtnggggtg	actntcaata	aactgcttcg	tc		402

<210> 29

<211> 175  
 <212> DNA  
 <213> Homo sapien

<400> 29  
 cggacggggca tgaccgggtcc ggtcagctgg gtggccagtt tcagttcttc agcagaactg 60  
 tctcccttct tggggggcga gggcttcctg ggggaagagga tgagtttgga gcggtactcc 120  
 ttcagccgct gcacgttggc ctgcaggagac tccgtggact tggtccgcct cctcg 175

<210> 30  
 <211> 360  
 <212> DNA  
 <213> Homo sapien

<400> 30  
 ttgtatttct tatgatctct gatgggttct tctcgaaaat gccaaagtga agactttgtg 60  
 gcatgctcca gatttaaact cagctgaggc tccctttgtt ttcagttcca tgtaacaact 120  
 tggaaggaaa cttcacggac aggaagactg ctggagaaga gaagcgtgtt agcccatttg 180  
 aggtctgggg aatcatgtaa agggtagcca gacctactt ttagttatct acatcaatga 240  
 gttctttcag ggaaccaaac ccagaattcg gtgcaaaaagc caaacatctt ggtgggattt 300  
 gataaatgcc ttgggacctg gagtgtctggg cttgtgcaca ggaagagcac cagccgctga 360

<210> 31  
 <211> 380  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (380)  
 <223> n = A,T,C or G

<400> 31  
 acgctctaag cctgtccacg agctcaatag ggaagcctgt gatgactaca gactttgcga 60  
 acgctacgcc atggtttatg gatacaatgc tgccataaan cgctacttca ggaagcgccg 120  
 agggaccnaa tgagactgag ggaagaaaaa aaatctcttt tttctggag gctggcacct 180  
 gattttgtat cccctgtgtn cagcattncn gaaatacata ggcttatata caatgcttct 240  
 ttctgtata ttctctgtc tggtgcacc ccttnttccc gccccagat tgataagtaa 300  
 tgaaagtgca ctgcagtnag ggtcaangga gactcancat atgtgattgt tccntnataa 360  
 acttctggtg tgatacttcc 380

<210> 32  
 <211> 440  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (440)  
 <223> n = A,T,C or G

<400> 32  
 gtgtatggga gcccctgact cctcacgtgc ctgatctgtg cccttgggtc caggtcaggc 60  
 ccacccctg cacctccacc tgccccagcc cctgcctctg cccaagtgg gccagctgc 120  
 cctcattct ggggtggatg atgtgacct cctnggggga ctgcggaagg gacaagggtt 180

```

ccctgaagtc ttacgggtcca acatcaggac caagtccecat ggacatgctg acaggggtccc      240
caggggagac cgtntcanta gggatgtgtg cctggctgtg tacgtgggtg tgcagtgcac      300
gtganaagca cgtggcggct tctggggggc atgtttgggg aaggaagtgt gcccncacc      360
cttggaagaac ctcagtcccn gtagccccct gccctggcac agcngcatnc acttcaaggg      420
caccctttgg ggggtggggg

```

```

<210> 33
<211> 345
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(345)
<223> n = A,T,C or G

```

```

<400> 33
tattttaaca atgtttatta ttcatattatc cctctataga accaccaccc acaccgagga      60
gattattttgg agtgggtccc aacctagggc ctggactctg aaatctaact cccacttcc      120
ctcattttgt gacttaggtg ggggcatggt tcagtcagaa ctggtgtctc ctattggatc      180
gtgcagaagg aggacctagg cacacacata tgggtggccac acccaggagg gttgattggc      240
aggttggaag acaaaagtct cccaataaag gcacttttac ctcaaagang ggggtgggagt      300
tggtctgctg ggaatgttgt tggtgggggtg gggaagantt atttc      345

```

```

<210> 34
<211> 440
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

```

```

<400> 34
tgtaattttt ttattggaaa acaaatatac aacttggaaat ggatttttgag gcaaattgtg      60
ccataagcag attttaagtg gctaaacaaa gtttaaaaaag caagtaacaa taaaagaaaa      120
tgttttctggt acaggaccag cagtacaaaa aaatagtgtg cgagtacctg gataatacac      180
ccgtttttgca atagtgaac ttttaagtac atattgttga ctgtccatag tccacgcaga      240
gttacaactc cacacttcaa caacaacatg ctgacagttc ctaaaagaaaa ctactttaaa      300
aaaggcataa ccagatggt ccttcatttg accaactcca tctnagttta gatgtgcaga      360
agggtttana ttttcccaga gtaagccnca tgcaacatgt tacttgatca attttctaaa      420
ataaggtttt aggacaatga

```

```

<210> 35
<211> 540
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(540)
<223> n = A,T,C or G

```

```

<400> 35

```

```

atagatggaa tttattaagc ttttcacatg tgatagcaca tagttttaat tgcacccaaa      60
gtactaacia aaactctagc aatcaagaat ggcagcatgt tattttataa caatcaacac      120
ctgtggcttt taaaatttgg ttttcataag ataatttata ctgaagtaaa tctagccatg      180
cttttaaaaa atgcttttagg tcaactccaag ctgggcagtt aacatttggc ataaacaata      240
ataaaacaat cacaatttaa taaataacia atacaacatt gtaggccata atcatatata      300
gtataaggga aaagggtggtg gtgttganta agcagttatt agaatagaat accttggcct      360
ctatgcaaat atgtctagac actttgatcc actcagccct gacattcagt tttcaaagtt      420
aggaaacagg ttctacagta tcattttaca gtttccaaca cattgaaaac aagtagaaaa      480
tgatganttg atttttatta atgcattaca tcttcaagan ttatcaccaa cccctcaggt      540

```

<210> 36

<211> 555

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(555)

<223> n = A,T,C or G

<400> 36

```

cttcgtgtgc ttgaaaattg gagcctgccc ctcgcccat aagcccttgt tgggaactga      60
gaagtgtata tggggcccaa nctactggtg ccagaacaca gagacagcag cccantgcaa      120
tgctgtcgag cattgcaaac gccatgtgtg gaactaggag gaggaatatt ccactctggc      180
agaaaccaca gcattgggtt ttttctactt gtgtgtctgg gggaatgaac gcacagatct      240
gtttgacttt gttataaaaa tagggctccc ccacctcccc cntttctgtg tncctttattg      300
tagcantgct gtctgcaagg gagcccttan cccctggcag acanactgc ttcagtgcct      360
ctttcctctc tgctaaatgg atgttgatgc actggaggtc ttttancctg cccctgcatg      420
gcncctgctg gaggaagana aaactctgct ggcctgaccc acagtttctt gactggangc      480
cntcaacctt cttggttgaa gccttggtct gacctgaca tntgcttggg cncctgggtng      540
gnctgggctt cttaa

```

<210> 37

<211> 280

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(280)

<223> n = A,T,C or G

<400> 37

```

ccaccgacta taagaactat gccctcgtgt attcctgtac ctgcacatc caactttttc      60
acgtggattt tgcttggatc ttggcaagaa accctaactt cctccagaa acagtggact      120
ctctaaaaaa tatcctgact tctaataaca ttgatntcaa gaaaatgacg gtcacagacc      180
aggtgaactg ccccnagctc tcgtaaccag gttctacagg gaggtgcac ccactccatg      240
ttnccttctg ttcgctttcc cctacccac cccccgccat

```

<210> 38

<211> 303

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(303)

<223> n = A,T,C or G

<400> 38

catcgagctg gttgtcttct tgctgacct	gtgtcgtaaa atgggggtcc cttactgcat	60
tatcaaggga aaggcaagac tgggacgtct	agtccacagg aagacctgca ccactgtcgc	120
cttcacacag gtgaactcgg aagacaaagg	cgctttggct nagctggtgn aagctatcag	180
gaccaattac aatgaatgat acgatnagat	ccgccntcac tggggtagca atgtcctggg	240
tcctaagtct gtggctcgta tcgccnagct	cgaanaggcn aangctaaag aacttgccac	300
taa		303

<210> 39

<211> 300

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(300)

<223> n = A,T,C or G

<400> 39

gactcagcgg ctggtgctct tcctgtgcac	aagcccagca ctccaggtcc caaggcattt	60
atcaaattccc accaagatnt ttggcttttg	caccgaattc tgggttttgt tccctnaaag	120
aactcattga tgtaaatnac tnaaagttag	gtctgggtac cctttacatg attccccaga	180
cctcanatgg gctaacacgc ttctcttctc	cagcagtcct cctntccgtg aagttacctt	240
ccagattggt acatggaact gaanacaaa	ggagcctcag ctngatttaa atctggagca	300

<210> 40

<211> 318

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(318)

<223> n = A,T,C or G

<400> 40

cccaacacaa tggctgagga caaatcagtt	ctctgtgacc agacatgaga aggttgccaa	60
tgggctgttg ggcgaccaag gccttcccgg	agtcttcgtc ctctatgagc tctcgcccat	120
gatggtgaag ctgacggaga agcacaggtc	cttcacccac ttctgacag gtgtgtgcgc	180
catcattggg ggcatgttca cagtggctgg	actcatcgat tcgctcatct accactcage	240
acgagccatc cagaaaaaaa ttgatctnng	gaagacnagc tagtcaccct cggtncttcc	300
tctgtctcct ctttctcc		318

<210> 41

<211> 302

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(302)

<223> n = A,T,C or G

<400> 41

```
acttagatgg ggtccgttca ggggatacca gcggttcacat ttttcctttt aagaaaggggt      60
cttggcctga atgttcccca tccggacaca ggctgcatgt ctctgttnagt gtcaaagctg      120
ccatnaccat ctcggttaacc tactcttact ccacaatgtc tatnttcact gcagggctct      180
ataatnagtc cataatgtaa atgcctggcc caagacntat ggcttgagtt tatccnaggc      240
ccaaacnatt accagacatt cctcttanat tgaaaacgga tntctttccc ttggcaaaga      300
tc                                                                                   302
```

<210> 42

<211> 299

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(299)

<223> n = A,T,C or G

<400> 42

```
cttaataagt ttaaggccaa ggcccgttcc attctttctag caactgacgt tgccagccga      60
ggtttggaca tacctcatgt aaatgtgggt gtcaaatttg acattcctac ccattccaag      120
gattacatcc atcgagtagg tcgaacagct agagctgggc gtcocggaaa ggctattact      180
tttgtcacac agtatgatgt ggaactcttc cagcgcatag aacacttnat tgggaagaaa      240
ctaccaggtt ttccaacaca ggatgatgag gttatgatgc tnacggaacg cgtcgctna      299
```

<210> 43

<211> 305

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(305)

<223> n = A,T,C or G

<400> 43

```
ccaacaatgt caagacagcc gtctgtgaca tcccacctcg tggcctcaan atggcagtc      60
ccttcattgg caatagcaca gccntccggg agctcttcaa ggcacatctcg gagcagttca      120
ctgccatggt ccgccggaag gccttccctcc actggtacac aggcgagggc atggacaaga      180
tggagttcac cgaggctgag agcaacatga acgacctcgt ctctnagtat cagcagtaacc      240
gggatgccac cgcagaaana ggaggaggat ttcggtnagg aggccgaaga aggaggcctg      300
aggca                                                                                   305
```

<210> 44

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(399)

<223> n = A,T,C or G

```

<400> 44
tttctgtggg ggaaacctga tctcgacnaa attagagaaat tttgtcagcg gtatttcggc      60
tggaacagaa cgaaaacnga tnaatctctg tttcctgtat taaagcaact cgatncccag      120
cagacacagc tccnaattga ttccttcttt ngattagcac aacagggaga aagaanatgc      180
ttaacgtatt aagagccnga gactaaacag agctttgaca tgtatgctta ggaaagagaa      240
agaagcagcn gcccgcgnaa ttngaagcng tttctgttgc cntgganaaa gaatttgagc      300
ttctttatta ggccaacgaa aaaccccga ananaggcnt tacnatacct tngaaaantc      360
tccngccenna aaaagaaaga agctttcnga ttcttaacc                               399

```

```

<210> 45
<211> 440
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

```

```

<400> 45
gcgggagcag aagctaaagc caaagcccaa gagagtggca gtgccagcac tggtgccagt      60
accagtacca ataacagtgc cagtgccagt gccagcacca gtgggtggctt cagtgtcgtg      120
gccagcctga ccgccactct cacatttggg ctcttcgctg gccttggtgg agctggtgcc      180
agcaccagtg gcagctctgg tgctgtgggt ttctcttaca agtgagattt taggtatctg      240
ccttggtttc agtggggaca tctggggcctt anggggcngg gataaggagc tggatgattc      300
taggaaggcc cangttggag aangatgtgn anagtgtgcc aagacactgc ttttggcatt      360
ttattccttt ctgtttgctg gangtcaatt gacccttnna ntttctctta cttgtgtttt      420
canatatngt taatcctgcc                               440

```

```

<210> 46
<211> 472
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 46
gctctgtaat ttcacatttt aaaccttccc ttgacctcac attcctcttc ggccacctct      60
gtttctctgt tctcttcac agcaaaaact gttcaaaaaga gttgttgatt actttcattt      120
ccactttctc acccccattc tccctcaat taactctcct tcatcccat gatgccatta      180
tgtggctntt attanagtca ccaaccttat tctccaaaac anaagcaaca aggactttga      240
cttctcagca gcactcagct ctggtncttg aaacaccccc gttacttgct attcctccta      300
cctcataaca atctccttcc cagcctctac tgctgccttc tctgagttct tcccagggtc      360
ctaggctcag atgtagtgta gctcaacct gctacacaaa gnaatctcct gaaagcctgt      420
aaaaatgtcc atnctgtgcc tgtgagtgat ctncangna naataacaaa tt                               472

```

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<210> 47
<211> 550
<212> DNA
<213> Homo sapien

```

```

<220>

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<221> misc\_feature  
 <222> (1)...(550)  
 <223> n = A,T,C or G

<400> 47  
 ccttcctccg cctggccatc cccagcatgc tcatgctgtg catggagtgg tgggcctatg 60  
 aggtcgggag cttcctcagt ggtctgtatg aggatggatg acggggactg gtgggaacct 120  
 gggggccctg tctgggtgca aggcgacagc tgtctttctt caccaggcat cctcggcatg 180  
 gtggagctgg gcgctcagtc catcgtgtat gaactggcca tcatttgtga catggtcctt 240  
 gcaggcttca gtgtggctgc cagtgtccgg gtangaaacg ctctgggtgc tggagacatg 300  
 gaagcaggca cggaaagtct ctaccgtttc cctgctgatt acagtgcctt ttgctgtanc 360  
 cttcagtgct ctgctgttaa gctgtaagga tcacntgggg tacattttta ctaccgaccg 420  
 agaacatcat taatctgggtg gctcaggtgg ttccaattta tgctgtttcc cacctctttg 480  
 aagctcttgc tgctcaggtg cagcccaatt ttgaaaagta aacaacgtgc ctcggaagtgg 540  
 gaattctgct 550

<210> 48  
 <211> 214  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(214)  
 <223> n = A,T,C or G

<400> 48  
 agaaggacat aaacaagctg aacctgccca agacgtgtga taccagcttc tcagatccag 60  
 acaacctcct caacttcaag ctggctcatct gtccatgatna gggcttctac nagagtggga 120  
 agttttgtgtt cagttttaag gtggggccagg gttaccgcga tgatcccccc aaggtgaagt 180  
 gtgagacnat ggtctatcac ccnaccattg acct 214

<210> 49  
 <211> 267  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(267)  
 <223> n = A,T,C or G

<400> 49  
 atctgcctaa aattttattca aataatgaaa atnaatctgt ttttaagaaat tcagtctttt 60  
 agtttttagg acaactatgc acaaatgtac gatggagaat tcttttttggga tnaactctag 120  
 gtngaggaac ttaatccaac cggagctntt gtgaagggtca gaanacagga gaggggaatct 180  
 tggcaaggaa tggagacnga gtttgcaaat tgcagctaga gtnaatngtt ntaaatggga 240  
 ctgctnttgt gtctcccang gaaagtt 267

<210> 50  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(300)  
 <223> n = A,T,C or G

<400> 50  
 gactgggtca aagctgcatg aaaccaggcc ctggcagcaa cctgggaatg gctggaggtg 60  
 ggagagaacc tgacttctct ttcctctctc ctccctccaac attactggaa ctctgtcctg 120  
 ttgggatctt ctgagcttgt ttccttgctg ggtgggacag aggacaaagg agaagggagg 180  
 gtctagaaga ggcagccctt ctttgtcctc tggggtnaat gagcttgacc tanagtagat 240  
 ggagagacca anagcctctg atttttaatt tccataanat gttcnaagta tatntntacc 300

<210> 51  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(300)  
 <223> n = A,T,C or G

<400> 51  
 gggtaaaatc ctgcagcacc cactctggaa aatactgctc ttaatttttc tgaaggtggc 60  
 cccctatttc tagttggtcc aggattaggg atgtggggta tagggcattt aaatcctctc 120  
 aagcgctctc caagcaccac cggcctgggg gtnagtttct catcccgcta ctgctgctgg 180  
 gatcaggttn aataaatgga actcttcctg tctggcctcc aaagcagcct aaaaactgag 240  
 gggctctgtt agaggggacc tccaccctnn ggaagtcgga ggggctnggg aagggtttct 300

<210> 52  
 <211> 267  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(267)  
 <223> n = A,T,C or G

<400> 52  
 aaaatcaact tcntgcatta atanacanat tctanancag gaagtgaana taattttctg 60  
 cacctatcaa ggaacnnact tgattgcctc tattnaacan atatatcgag ttntataact 120  
 tacctgaata ccnccgcata actctcaacc nanatnctc nccatgacac tcnttcttna 180  
 atgctantcc cgaattcttc attatatcng tgatgttcgn cctgntnata tatcagcaag 240  
 gtatgtncnn taactgccga nncaang 267

<210> 53  
 <211> 401  
 <212> DNA  
 <213> Homo sapien

<400> 53  
 agscitttagc atcatgtaga agcaaactgc acctatggct gagataggtg caatgacctc 60  
 caagattttg tgttttctag ctgtccagga aaagccatct tcagtcttgc tgacagtcaa 120  
 agagcaagtg aaaccatttc cagcctaaac tacataaaaag cagccgaacc aatgattaaa 180  
 gacctctaag gctccataat catcattaaa tatgcccaa ctcattgtga ctttttattt 240

tatatacagg	attaaaatca	acattaaatc	atcttattta	catggccatc	gggtgctgaaa	300
ttgagcattt	taaatagtag	agtaggctgg	tatacattag	gaaatggact	gcactggagg	360
caaatagaaa	actaaagaaa	ttagataggc	tggaaatgct	t		401

&lt;210&gt; 54

&lt;211&gt; 401

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 54

cccaacacaa	tggataaaaa	cacttatagt	aaatggggac	attcactata	atgatctaag	60
aagctacaga	ttgtcatagt	tgttttcctg	ctttacaaaa	ttgctccaga	tctggaatgc	120
cagtttgacc	tttgtcttct	ataatatttc	ctttttttcc	cctctttgaa	tctctgtata	180
tttgattctt	aactaaaatt	gttctcttaa	atattctgaa	tcctggtaat	taaaagtgtg	240
gggtgatttt	ctttacctcc	aaggaaaagaa	ctactagcta	caaaaaatat	tttggaataa	300
gcattgtttt	ggtataaggt	acatattttg	gttgaagaca	ccagactgaa	gtaaacagct	360
gtgcatccaa	tttattatag	ttttgtaagt	aacaatatgt	a		401

&lt;210&gt; 55

&lt;211&gt; 933

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 55

tttactgctt	ggcaaagtac	cctgagcatc	agcagagatg	ccgagatgaa	atcaggggaa	60
tcctagggga	tgggtcttct	attacctggg	aacacctgag	ccagatgcct	tacaccacga	120
tgtgcatcaa	ggaatgcctc	cgctctacg	caccggtagt	aaactatccc	ggttactcga	180
caaaccatc	acctttccag	atggacgctc	cttacctgca	ggaataactg	tgtttatcaa	240
tatttgggct	cttcaccaca	acctctat	ctgggaagac	cctcaggtct	ttaaccctt	300
gagattctcc	agggaaaatt	ctgaaaaaat	acatccctat	gccttcatac	cattctcagc	360
tggattaagg	aactgcattg	ggcagcattt	tgccataatt	gagtgtaaag	tggcagtggt	420
attaactctg	ctccgcttca	agctggctcc	agaccactca	aggccacca	gctgtcgtca	480
agttgcctca	agtccaagaa	tggaaatccat	gtgtttgcaa	aaaaagtgtg	ctaattttaa	540
gtccttttctg	tataagaatt	aakgagacaa	ttttcctacc	aaaggaagaa	caaaaggata	600
aatataatac	aaaatatatg	tatatggttg	tttgacaaat	tatataactt	aggatacttc	660
tgactgggtt	tgacatccat	taacagtaat	tttaatttct	ttgctgtatc	tgggtgaaacc	720
cacaaaaaca	cctgaaaaaa	ctcaagctga	gttccaatgc	gaagggaaat	gattgggttg	780
ggtaactagt	ggtagagtgg	ctttcaagca	tagtttgatc	aaaactccac	tcagtatctg	840
cattactttt	atctctgcaa	atatctgcat	gatagcttta	ttctcagtta	tctttcccca	900
taataaaaaa	tatctgccaa	aaaaaaaaaa	aaa			933

&lt;210&gt; 56

&lt;211&gt; 480

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 56

ggctttgaag	catttttgtc	tgtgctccct	gatcttcagg	tcaccaccat	gaagtcttta	60
gcagtcctgg	tactcttggg	agttttccatc	tttctgggtct	ctgccagaa	tccgacaaca	120
gctgctccag	ctgacacgta	tccagctact	ggtcctgctg	atgatgaagc	ccctgatgct	180
gaaaccactg	ctgctgcaac	cactgcgacc	actgctgctc	ctaccactgc	aaccaccgct	240
gcttctacca	ctgctcgtaa	agacattcca	gttttaccca	aatgggttgg	ggatctcccg	300
aatggtagag	tgtgtccctg	agatggaatc	agcttgagtc	ttctgcaatt	ggtcacaact	360
attcatgctt	cctgtgattt	catccaacta	cttaccttgc	ctacgatatc	ccctttatct	420
ctaatacagtt	tattttcttt	caaataaaaa	ataactatga	gcaacaaaaa	aaaaaaaaaa	480

<210> 57  
 <211> 798  
 <212> DNA  
 <213> Homo sapien

<400> 57  
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 gactaacttt gtgatatggg aagtgaaaat agttaacacc ttgcacgacc aaacgaacga 120  
 agatgaccag agtactctta accccttaga actgtttttc cttttgtatc tgcaatatgg 180  
 gatgggtattg ttttcatgag cttctagaaa ttccacttgc aagtttattt ttgcttcctg 240  
 tgttactgcc attcctatct acagtatatt tgagtgaatg attatatttt taaaaagtta 300  
 catggggcctt ttttgggtgt cctaaactta caaacattcc actcattctg tttgtaactg 360  
 tgattataat ttttgtgata atttctggcc tgattgaagg aaatttgaga ggtctgcatt 420  
 tatatatattt aaatagattt gataggtttt taaattgctt tttttcataa ggtattttata 480  
 aagttatttg gggttgtctg ggatttgtgt aaagaaaatt agaaccctgc tgtattttaca 540  
 tttaccttgg tagtttattt gtggatggca gttttctgta gttttgggga ctgtggtagc 600  
 tcttggtattg ttttgcaaat tacagctgaa atctgtgtca tggattaaac tggcttatgt 660  
 ggctagaata ggaagagaga aaaaatgaaa tgggtgttta ctaattttat actcccatta 720  
 aaaattttta atgttaagaa aaccttaaat aaacatgatt gatcaatatg gaaaaaaaaa 780  
 aaaaaaaaaa aaaaaaaaaa 798

<210> 58  
 <211> 280  
 <212> DNA  
 <213> Homo sapien

<400> 58  
 ggggcagctc ctgacctcc acagccacct ggtcagccac cagctggggc aacgaggggtg 60  
 gaggtccac tgagcctctc gctgcccc gccactcgtc tgggtgcttg tgatccaagt 120  
 cccctgcttg gtccccaca aggactcca tccaggcccc ctctgccctg ccccttgta 180  
 tggaccatgg tcgtgaggaa gggctcatgc cccttattta tgggaaccat ttcattctaa 240  
 cagaataaac cgagaaggaa accagaaaaa aaaaaaaaaa 280

<210> 59  
 <211> 382  
 <212> DNA  
 <213> Homo sapien

<400> 59  
 aggcgggagc agaagctaaa gccaaagccc aagagagtgg cagtgccagc actggtgcca 60  
 gtaccagtac caataacagt gccagtgcc gtgccagcac cagtgggtggc ttcagtgtg 120  
 gtgccagcct gaccgccact ctcacatttg ggtctttcgc tggccttggt ggagctgggt 180  
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt 240  
 gttaatcctg ccagtctttc ttttcaagcc aggggtgcac ctcagaaacc tactcaacac 300  
 agcactctag gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg 360  
 ccattaaaaa aaaaaaaaaa aa 382

<210> 60  
 <211> 602  
 <212> DNA  
 <213> Homo sapien

<400> 60  
 tgaagagccg cgcgggtggag ctgctgcccc atgggactgc caaccttgcc aagctgcagc 60

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gagatgtgtc ccggctggcc tacacccagc gcatacctgga gatcgtgggc aacatccgga 360
agcagaagga agagatcacc aagatcttgt ctgatacgaa ggagcttcag aaggaaatca 420
actccctatc tgggaagctg gaccggacgt ttgcggtgac tgatgagctt gtgttcaagg 480
atgccaaaga ggacgatgct gttcggaagg cctataagta tctagctgct ctgcacgaga 540
actgcagcca gctcatccag accatcgagg acacaggcac catcatgcgg gaggttcgag 600
ac 602

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<210> 61

<211> 1368

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1368)

<223> n = A,T,C or G

<400> 61

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ccagtgaagc cgcgtaatac gactcactat agggcgaatt gggtagcggg cccccctcg 60
agcgcccgcc cttttttttt tttttttatt gatcagaatt caggctttat tattgagcaa 120
tgaaaacagc taaaacttaa ttccaagcat gtgtagttaa agtttgcaaa gtgggatatt 180
gttcacaaaa cacattcaat gtttaaacac tatttatttg aagaacaaaa tatattttaa 240
attgtttgct tctaaaaagc ccatttccct ccaagtctaa actttgtaat ttgatattaa 300
gcaatgaagt tattttgtac aatctagtta aacaagcaga atagcactag gcagaataaa 360
aaattgcaca gacgtatgca attttccaag atagcattct ttaaattcag ttttcagctt 420
ccaaagattg gttgcccata atagacttaa acatataatg atggctaaaa aaaataagta 480
tacgaaaatg taaaaaagga aatgtaagtc cactctcaat ctcataaaaag gtgagagtaa 540
ggatgctaaa gcaaaaataaa tgtagggtct ttttttctgt ttccgtttat catgcaatct 600
gcttctttga tatgccttag ggttaccat ttaagttaga ggttgtaatg caatgggtgg 660
aatgaaaatt gatcaaatat acaccttgtc atttcatttc aaattgcggg ctggaaactt 720
ccaaaaaaag ggtaggcatg aagaaaaaaa aaatcmaatc agaacctctt caggggtttg 780
kgktctgata tggcagacar gatacaagtc ccaccaggag atggagcaat tcaaaaataag 840
ggtaatgggc tgacaaggta ttattgccag catgggacag aatgagcaac aggctgaaaa 900
gtttttggat tatatagcac cttagagctc tgatgtaggg aatttttgtt agtcaaact 960
acgctaaact tccaaggga aatctttcag gtagcctaag cttgcttttc tagagtgatg 1020
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tatttctgat cccctatacc ccaggaaggg caaaatccca aagaaatgtg ttagcaaaat 1200
tggctgatgc tatcatattg ctatggacat tgatcttgcc caacacaatg gaattccacc 1260
acactggact agtggatcca ctagtcttag agcgccgggc caccgcggtg gagctccagc 1320
ttttgttccc tttagttagg gttaattgcg cgcttggcgt aatcatnn 1368

```

<210> 62

<211> 924

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(924)

<223> n = A,T,C or G

&lt;400&gt; 62

caaaggnaca	ggaacagctt	gnaaagtact	gncatnccn	cctgcagggg	ccagcccttt	60
gcctccaaaa	gcaataggaa	attttaaaga	tttncaactga	gaaggggncc	acgttttnart	120
tntnaatgtn	tcargnanar	tnccctncaa	atgnernctn	cactnactnr	gnattttgggt	180
tnccgnrtnc	mgnactatnt	cagggtttgaa	aaactggatc	tgccacttat	cagttatgtg	240
accttaaaga	actccgttaa	tttctcagag	cctcagtttc	cttgtctata	agttgggagt	300
aatattaata	ctatcatttt	tccaaggatt	gatgtgaaca	ttaatgaggt	gaaatgacag	360
atgtgtatca	tggttcctaa	taaacatcca	aaatatagta	cttactattg	tcattattat	420
tacttgtttg	aagctaaaga	cctcacaata	gaatcccatc	cagcccacca	gacagagytc	480
tgagttttct	agtttggaag	agctattaaa	taacaacktc	tagtgtcaat	tctatacttg	540
ttatgggtcaa	gtaactgggc	tcagcatttt	acattcattg	tctctttaag	ttctagcaat	600
gtgaagcagg	aactatgatt	atattgacta	cataaatgaa	gaaattgagg	ctcagatata	660
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gggaatcact	gcacgtcgca	agagatgttg	cttctgatga	attattgttc	ctgtcagtgg	900
tgtgaaggca	aaaaaaaaaa	aaaa				924

&lt;210&gt; 63

&lt;211&gt; 1079

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 63

agtcaccaaga	actcaataat	ctcttatgtt	ttcttttgaa	gacttatttt	aaatattaac	60
tatttcggtg	cctgaatgga	aaaatataaa	cattagctca	gagacaatgg	ggtacctgtt	120
tggaatccag	ctggcagcta	taagcacogt	tgaaaactct	gacaggcttt	gtgccctttt	180
tattaaatgg	cctcacatcc	tgaatgcagg	aatgtgttcg	tttaaataaa	cattaatctt	240
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acaatcaggg	caaaacccac	acttgaaaag	cattttacaa	tattatatct	aagttgcaca	420
gaagacccca	gtgatcacta	ggaaatctac	cacagtcacg	tttttctaata	ccaagaaggt	480
caaacttcgg	ggaataatgt	gtccctcttc	tgctgctgct	ctgaaaaata	ttcgatcaaa	540
acgaagttta	caagcagcag	ttattccaag	attagagttc	atttgtgtat	cccatgtata	600
ctggcaatgt	ttagggtttg	ccaaaaactc	ccagacatcc	acaatgttgt	tgggtaaacc	660
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ttggcttttt	aatttcactc	ttgatttctt	caacattata	gctgtgaaat	atccttcttc	960
atgacctgta	ataatctcat	aattacttga	tctcttcttt	aggtagctat	aatatggggg	1020
aataacttcc	tgtagaataa	tcacatctgg	gctgtacaaa	gctaagtagg	aacacacccc	1079

&lt;210&gt; 64

&lt;211&gt; 1001

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 64

gaatgtgcaa	cgatcaagtc	agggtatctg	tggtatccac	cactttgagc	atttatcgat	60
tctatatgtc	aggaacattt	caagttatct	gttctagcaa	ggaaatataa	aatacttata	120
gttaactatg	gcctatctac	agtgcacta	aaaactagat	tttattcctt	tccacctgtg	180
ggtttgatt	catttaccac	cctcttttca	ttccctttct	cacccacaca	ctgtgccggg	240
cctcaggcat	atactattct	actgtctgtc	tctgtaagga	ttatcatttt	agcttcacac	300

tatgagagaa	tgcattgcaaa	gttttttcttt	ccatgtcttgg	cttattttcac	ttaacataat	360
gacctccgct	tccatccatg	ttattttatat	tacccaatag	tgttcataaa	tatatataca	420
cacatatata	ccacattgca	tttgtccaat	tattcattga	cggaaactgg	ttaatgttat	480
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tttgatggta	ttaatTTTTT	cattccatga	agatgagatg	tctttccatt	gtttgtgtcc	720
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agatcaagtg	tattccctaa	atattttatt	tttgtagcta	ttgtagatga	aattgccttc	840
ttgatttcct	tttcacttaa	ttcattatta	gtgtatggaa	atgttatgga	tttttatttg	900
ttggttttta	atcaaaaact	gtattaaact	tagagttttt	tgtggagttt	ttaagttttt	960
ctagatataa	gatcatgaca	tctacccaaa	aaaaaaaaaa	a		1001

&lt;210&gt; 65

&lt;211&gt; 575

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 65

acttgatata	aaaaggatat	ccataatgaa	tattttatac	tgcattccttt	acattagcca	60
ctaaatacgt	tattgcttga	tgaagacctt	tcacagaatc	ctatggattg	cagcatttca	120
cttggctact	tcatacccat	gccttaaaga	ggggcagttt	ctcaaaaagca	gaaacatgcc	180
gccagttctc	aagttttcct	cctaactcca	tttgaatgta	agggcagctg	gccccaatg	240
tggggagggtc	cgaacatttt	ctgaattccc	attttcttgt	tcgcggctaa	atgacagttt	300
ctgtcattac	ttagattccc	gatctttccc	aaagggtgtg	atttacaag	aggccagcta	360
atagccagaa	atcatgaccc	tgaaagagag	atgaaatttc	aagctgtgag	ccaggcagga	420
gctccagtat	ggcaaaagggt	cttgagaatc	agccatttgg	tacaaaaaag	atttttaag	480
cttttatgtt	ataccatgga	gccatagaaa	ggctatggat	tgtttaagaa	ctatttttaa	540
gtgttccaga	cccaaaaagg	aaaaaaaaaa	aaaaa			575

&lt;210&gt; 66

&lt;211&gt; 831

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 66

attgggctcc	ttctgctaaa	cagccacatt	gaaatggttt	aaaagcaagt	cagatcaggt	60
gatttgtaaa	attgtattta	tctgtacatg	tatgggcttt	taattcccac	caagaaagag	120
agaaattatc	tttttagtta	aaaccaaatt	tcacttttca	aaatatcttc	caacttattt	180
attggttgtc	actcaattgc	ctatatatat	atatatatat	gtgtgtgtgt	gtgtgtgcgc	240
gtgagcgcac	gtgtgtgtat	gcgtgcgcat	gtgtgtgtat	gtgtattatc	agacataggt	300
ttctaacttt	tagatagaag	aggagcaaca	tctatgccaa	atactgtgca	ttctacaatg	360
gtgctaattc	cagacctaaa	tgatactcca	tttaatttaa	aaaagagttt	taaataatta	420
tctatgtgcc	tgtattttccc	ttttgagtgc	tgacacacat	gttaacatat	tagtgtaaaa	480
gcagatgaaa	caaccacgtg	ttctaaaagtc	tagggattgt	gctataatcc	ctattttagt	540
caaaattaac	cagaattctt	ccatgtgaaa	tggaccaaac	tcatattatt	gttatgtaaa	600
tacagagttt	taatgcagta	tgacatccca	caggggaaaa	gaatgtctgt	agtgggtgac	660
tgttatcaaa	tattttatag	aatacaatga	acgggtgaaca	gactggtaac	ttgtttgagt	720
tcccatgaca	gatttgagac	ttgtcaatag	caaatcattt	ttgtatttaa	atttttgtac	780
tgatttgaaa	aacatcatta	aatatcttta	aaagtaaaaa	aaaaaaaaaa	a	831

&lt;210&gt; 67

&lt;211&gt; 590

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

```

<400> 67
gtgctctgtg tattttttta ctgcattaga cattgaatag taatttgctg taagatacgc      60
ttaaaggctc ttgtgacca tgtttccctt tgtagcaata aaatgttttt tacgaaaact      120
ttctccctgg attagcagtt taaatgaaac agagttcatc aatgaaatga gtatttataaa      180
taaaaatttg ccttaatgta tcagttcagc tcacaagtat ttttaagatga ttgagaagac      240
ttgaattaaa gaaaaaaaaa ttctcaatca tttttttaa atataagact aaaattgttt      300
ttaaaccaca ttcaaataag aagtgagttt gaactgacct tattttatact ctttttaagt      360
ttgttccctt tccctgtgcc tgtgtcaaat cttcaagtct tgctgaaaat acatttgata      420
caaagttttc tgtagttgtg ttagttcttt tgtcatgtct gtttttggct gaagaaccaa      480
gaagcagact tttcttttaa aagaattatt tctctttcaa atatttctat cttttttaa      540
aaattccctt ttatggctta tataacctaca tatttaaaaa aaaaaaaaaa      590

```

<210> 68

<211> 291

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(291)

<223> n = A,T,C or G

```

<400> 68
gttccctttt ccggctcggcg tggctcttgcg agtggagtggt ccgctgtgcc cgggcctgca      60
ccatgagcgt cccggccttc atcgacatca gtgaagaaga tcaggctgct gagcttcgtg      120
cttatctgaa atctaaagga gctgagattt cagaagagaa ctcggaagggt ggacttcatg      180
ttgatttagc tcaaattatt gaagcctgtg atgtgtgtct gaaggaggat gataaagatg      240
ttgaaagtgt gatgaacagt ggggnatcct actcttgatc cggaanccna c      291

```

<210> 69

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(301)

<223> n = A,T,C or G

```

<400> 69
tctatgagca tgccaaggct ctgtgggagg atgaaggagt gcgtgcctgc tacgaacgct      60
ccaacgagta ccagctgatt gactgtgccc agtacttcct ggacaagatc gacgtgatca      120
agcaggctga ctatgtgccg agcgatcagg acctgcttcg ctgccgtgtc ctgacttctg      180
gaatctttga gaccaagttc caggtggacn aagtcaactt ccacatgntt gacgtgggtg      240
gccagcgcga tgaacgcgcg aagtggatcc agtgcttcaa cgatgtgact gccatcatct      300
t

```

<210> 70

<211> 201

<212> DNA

<213> Homo sapien

<400> 70

```

gcggctcttc ctcgggcagc ggaagcggcg cggcggtcgg agaagtggcc taaaacttcg      60

```

```

gcgttgggtg aaagaaaatg gcccgaaacca agcagactgc tcgtaagtcc accggtggga      120
aagccccccg caaacagctg gccacgaaag ccgccaggaa aagcgctccc tctaccggcg      180
gggtgaagaa gcctcatcgc t                                     201

```

```

<210> 71
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 71
gccggggtag tcgccgnccg ccgccccgct gcagccactg caggcaccgc tgccgccgcc      60
tgagttagtgg gcttaggaag gaagagggtca tctcgctcgg agcttcgctc ggaagggtct      120
ttgttccttg cagccctccc accggaatga caatggataa aagtgaagctg gtacanaaag      180
ccaaactcgc tgagcaggct gagcgatatg atgatatggc tgcagccatg aaggcagtca      240
cagaacaggg gcatgaactc ttcaacgaag agagaaatct gctctctggt gcctacaaga      300
a                                     301

```

```

<210> 72
<211> 251
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(251)
<223> n = A,T,C or G

```

```

<400> 72
cttgggggggt gttggggggag agactgtggg cctggaaata aaacttgtct cctctaccac      60
cacctgttac cctagcctgc acctgtccac atctctgcaa agttcagctt ccttccccag      120
gtctctgtgc actctgtctt ggatgctctg gggagctcat ggttggagga gtctccacca      180
gagggaggct caggggactg gttggggccag ggatgaatat ttgagggata aaaattgtgt      240
aagagccaan g                                     251

```

```

<210> 73
<211> 895
<212> DNA
<213> Homo sapien

```

```

<400> 73
tttttttttt tttttcccag gccctctttt tatttacagt gataccaaac catccacttg      60
caaattcttt ggtctcccat cagctggaat taagtaggta ctgtgtatct ttgagatcat      120
gtatttgtct ccactttggt ggatacaaga aaggaaggca cgaacagctg aaaaagaagg      180
gtatcacacc gctccagctg gaatccagca ggaacctctg agcatgccac agctgaacac      240
ttaaaagagg aaagaaggac agctgctctt catttatctt gaaagcaaatt tcatttgaaa      300
gtgcataaat ggtcatcata agtcaaacgt atcaattaga ccttcaacct aggaacacaa      360
atTTTTTTTT tctatttaat aatacaccac actgaaatta tttgccaatg aatcccaaag      420
atttgggtaca aatagtacaa ttcgtatttg ctttctctct tctttctctc agacaaacac      480
caaataaaat gcagggtgaaa gagatgaacc acgactagag gctgacttag aaatttatgc      540
tgactcgatc taaaaaaaaat tatgttgggt aatgttaatc tatctaaaat agagcatttt      600

```

```

gggaatgctt ttcaaagaag gtcaagtaac agtcatacag ctagaaaagt ccoetgaaaaa 660
aagaattggt aagaagtata ataacctttt caaaacccac aatgcagctt agttttcctt 720
tattttattg tgggtcatgaa gactatcccc atttctccat aaaatcctcc ctccatactg 780
ctgcattatg gcacaaaaga ctctaagtgc caccagacag aaggaccaga gtttctgatt 840
ataaacaatg atgctgggta atgtttaaat gagaacattg gatatggatg gtcag 895

```

```

<210> 74
<211> 351
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(351)
<223> n = A,T,C or G

```

```

<400> 74
tgtgcnacagg ggatgggtgg gcngtggaga ngatgacaga aaggctggaa ggaanggggg 60
tggttttgaa ggccangggc aaggggncct caggtccgnt tctgnnaagg gacagccttg 120
aggaaggagn catggcaagc catagctagg ccaccaatca gattaagaaa nctgagaaa 180
nctagctgac catcactgtt ggtgnccagt ttcccaacac aatgggaatnc caccacactg 240
gactagnnga nccactagtt cttagagcggc cggccaccgg gtgggaacccc aacttttgcc 300
cctttagnga ggggttaattg cgcgcttggc ntaatcatgg tcataagctg t 351

```

```

<210> 75
<211> 251
<212> DNA
<213> Homo sapien

```

```

<400> 75
tacttgacct tctttgaaaa gcattcccaa aatgctctat tttagataga ttaacattaa 60
ccaacataat tttttttaga tcgagtcagc ataaatttct aagtcagcct ctagtcgtgg 120
ttcatctctt tcacctgcat tttatttggg gtttgtctga agaaaggaaa gaggaaagca 180
aatacgaatt gtactatttg taccaaatct ttgggattca ttggcaaata atttcagtgt 240
gggtgtattat t 251

```

```

<210> 76
<211> 251
<212> DNA
<213> Homo sapien

```

```

<400> 76
tatttaataa tacaccacac tgaaattatt tgccaatgaa tcccaaagat ttggtacaaa 60
tagtacaatt cgtattttgct ttctcttttc ctttcttcag acaaacacca aataaaatgc 120
aggtgaaaga gatgaaccac gactagaggc tgacttagaa atttatgctg actcgatcta 180
aaaaaaatta tgttgggttaa tgtaaatcta tctaaaatag agcatttttg gaatgctttt 240
caaagaaggt c 251

```

```

<210> 77
<211> 351
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature

```

&lt;222&gt; (1)...(351)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 77

actcaccgtg	ctgtgtgctg	tgtgcctgct	gcctggcagc	ctggccctgc	cgctgctcag	60
gaggcgggag	gcatgagtga	gctacagtgg	gaacaggctc	aggactatct	caagagannn	120
tatctctatg	actcagaaac	aaaaaatgcc	aacagtttag	aagccaaact	caaggagatg	180
caaaaattct	ttggcctacc	tataactgga	atgttaaact	cccgcgtcat	agaaataatg	240
cagaagccca	gatgtggagt	gccagatggt	gcagaatact	cactatttcc	aaatagccca	300
aaatggactt	ccaaagtggg	cacctacagg	atcgtatcat	atactcgaga	c	351

&lt;210&gt; 78

&lt;211&gt; 1574

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 78

gccctggggg	cggaggggag	gggcccacca	cggccttatt	tccgcgagcg	ccggcactgc	60
ccgctccgag	cccggtgtctg	tccgggtgccg	agccaacttt	cctgcgtcca	tgcagccccc	120
ccggcaacgg	ctgcccgtctc	cctgggtccgg	gcccaggggc	ccgcgcccc	ccgccccgct	180
gctcgcgctg	ctgctgtttg	tcccccggg	ggcggcgccc	gcgggggtccg	gggaccccga	240
cgaccctggg	cagcctcagg	atgctggggg	cccgcgccag	ctcctgcagc	aggcggcgcg	300
cgcggcgctt	cacttcttca	acttccgggtc	cggctcgccc	agcgcgctgc	gagtgtgtgg	360
cgagggtgcag	gagggccgcg	cgtggattaa	tccaaaagag	ggatgtaaag	ttcacgtggg	420
cttcagcaca	gagcgctaca	accagagctc	tttacttcag	gaagggtgagg	gacgtttggg	480
gaaatgttct	gctcgagtgt	ttttcaagaa	tcagaaaacc	agaccaacta	tcaatgtaac	540
ttgtacacgg	ctcatcgaga	aaaagaaaag	acaacaagag	gattacctgc	tttacaagca	600
aatgaagcaa	ctgaaaaacc	ccttggaat	agtcagcata	cctgataatc	atggacatat	660
tgatccctct	ctgagactca	tctgggattt	ggctttcctt	ggaagctctt	acgtgatgtg	720
ggaaaatgaca	acacaggtgt	cacactacta	cttggcacag	ctcactagt	tgaggcagtg	780
gaaaactaat	gatgatacaa	ttgattttga	ttatactgtt	ctacttcatg	aattatcaac	840
acaggaaata	attccctgtc	gcattcactt	ggtctggtac	cctggcaaac	ctcttaaagt	900
gaagtaccac	tgtcaagagc	tacagacacc	agaagaagcc	tccggaactg	aagaaggatc	960
agctgtagta	ccaacagagc	ttagtaattt	ctaaaaagaa	aaaatgatct	ttttccgact	1020
tctaaacaag	tgactatact	agcataaatc	attcttctag	taaaacagct	aaggatataga	1080
catttctaata	atttgggaaa	acctatgatt	acaagtaaaa	actcagaaat	gcaaagatgt	1140
tggttttttg	tttctcagtc	tgttttagct	tttaactctg	gaagcgcag	cacactgaac	1200
tctgctcagt	gctaaacagt	caccagcagg	ttcctcaggg	tttcagccct	aaaatgtaaa	1260
acctggataa	tcagtgtatg	ttgcaccaga	atcagcattt	tttttttaac	tgcaaaaaat	1320
gatggtctca	tctctgaatt	tatatctctc	attcttttga	acatactata	gctaataat	1380
tttatgttgc	ttaaattgctt	ctatctagca	tgttaaacaa	agataatata	ctttcgatga	1440
aagtaaatga	taggaaaaaa	attaactgtt	ttaaaaagaa	cttgattatg	ttttatgatt	1500
tcaggcaagt	attcattttt	aacttgctac	ctacttttaa	ataaatgttt	acattttctaa	1560
aaaaaaaaaa	aaaa					1574

&lt;210&gt; 79

&lt;211&gt; 401

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(401)

&lt;223&gt; n = A,T,C or G

<400> 79							
catactgtga	attgttcttg	actccttttc	ttgacattca	gttttcanaa	tttccatctt		60
tcttctggaa	ctaattgtgct	gttctcttga	ctgcctgctg	ggccagcatc	cgattgccag		120
ccagaaacgt	cacactgcc	aagatggcca	ggtacttcaa	ggtctggaac	atggtgagct		180
gagtcacagta	gacatacatg	agtcccagca	tagcagcatg	tcccaggtga	aatataatcg		240
tgctaggagc	aaaagtgaag	ttggagacat	tggcaccaat	ccggaaccac	tagttctaga		300
cggcccgcca	ccgcggtgga	gtctcagctt	ttgttccctt	tagtgagggt	taattgcgcg		360
cttgqcgtaa	tcattggnat	agctgtttcc	tgtgtgaaat	t			401

```
<210> 80
<211> 301
<212> DNA
<213> Homo sapien
```

<400>	80						
aaaaatgaaa	catctatttt	agcagcaaga	ggctgtgagg	gatggggtag	aaaagggcatc		60
ctgagagagt	tctagaccga	cccaggtcct	gtggcacact	atacgggtca	ggaggggtgg		120
aagacaggcc	taagctctag	gacggtgaat	ctcggggcta	tttgtggatt	tgttagaaac		180
agacattctt	ttggcctttt	cctggcactg	gtgttgccgg	caggtgggca	gaagtgagcc		240
accagtcact	gttcagtcac	tgccaccaca	gatcttcagc	agaatcttcc	ggtaatcccc		300
t							301

```
<210> 81
<211> 301
<212> DNA
<213> Homo sapien
```

```
<220>  
<221> misc_feature  
<222> (1)...(301)  
<223> n = A,T,C or G
```

<400>	81						
tagccagggtc	gctcaagcta	atttttattct	ttcccaacag	gatccatttg	gaaaatatca		60
agccttttaga	atgtggcagc	aagagaaaagc	ggactacgca	ggaacgggga	gtttgggaga		120
agctctcctg	gtgttgactt	agggatgaag	gctccaggct	gctgccagaa	atggagtcac		180
cagcagaaga	actgntttct	ctgataagga	tgtcccacca	ttttcaagct	gttcgttaaa		240
gttacacagg	tctttcttgc	agcagtaagt	accgttagct	cattttccct	caagcggggt		300
t							301

```
<210> 82
<211> 201
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(201)
<223> n = A,T,C or G
```

```

<400> 82
tcaacagaca aaaaaagttt attgaataca aaactcaaag gcatcaacag tcctgggccc      60
aagagatcca tggcaggaag tcaagagttc tgcttcaggg tcgggtctggg cagccctgga      120
agaagtcatt gcacatgaca gtgatgagtg ccaggaaaac agcatactcc tggaaagtcc      180
acctctctgn cactgnttca t                                     201

```

<210> 83  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(251)  
 <223> n = A,T,C or G

<400> 83  
 gtaaggagca tactgtgccc atttattata gaatgcagtt aaaaaaata ttttgaggtt 60  
 agcctctcca gtttaaaagc acttaacaag aaacacttgg acagcgatgc aatgggtctct 120  
 cccaaaccgg ctccctctta ccaagtaccg taaacagggt ttgagaacgt tcaatcaatt 180  
 tcttgatatg aacaatcaaa gcattttaatg caaacatatt tgcttctcaa anaataaaac 240  
 cattttccaa a 251

<210> 84  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 84  
 agtttataat gttttactat gatttagggc ttttttttca aagaacaaaa attataagca 60  
 taaaaactca ggtatcagaa agactcaaaa ggctgttttt cactttgttc agattttggt 120  
 tccaggcatt aagtgtgtca tacagttgtt gccactgctg ttttccaaat gtccgatgtg 180  
 tgctatgact gacaactact tttctctggg tctgatcaat tttgcagtan accatttttag 240  
 ttcttacggc gtcnataaca aatgcttcaa catcatcagc tccaatctga agtcttgctg 300  
 c 301

<210> 85  
 <211> 201  
 <212> DNA  
 <213> Homo sapien

<400> 85  
 tatttggtga tgtaacattt attgacatct acccactgca agtatagatg aataagacac 60  
 agtcacacca taaaggagtt tatccttaaa aggagtgaaa gacattcaaa aaccaactgc 120  
 aataaaaaaag ggtgacataa ttgctaaatg gagtggagga acagtgttta tcaattcttg 180  
 attgggccac aatgatatac c 201

<210> 86  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)

<223> n = A,T,C or G

<400> 86

```

tttataaaat attttatttta cagtagagct ttacaaaaat agtctttaa taatacaaat      60
cccttttgca atataactta tatgactatc ttctcaaaaa cgtgacattc gattataaca      120
cataaactac attttatagtt gttaagtcac cttgtagtat aaatatgttt tcattcttttt      180
tttgtaataa ggtacatacc aataacaatg aacaatggac aacaaatctt attttgntat      240
tcttccaatg taaaattcat ctctggccaa aacaaaatta accaaagaaa agtaaaacaa      300
t                                                                    301

```

<210> 87

<211> 351

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(351)

<223> n = A,T,C or G

<400> 87

```

aaaaaagatt taagatcata aatagggtcat tgttgtcaca acacatttca gaatcttaaa      60
aaaacaaaca ttttggtttt ctaagaaaaa gactttttaa aaaaatcaat tccctcatca      120
ctgaaaggac ttgtacattt ttaaacttcc agtctcctaa ggcacagtat ttaatcagaa      180
tgccaatatt accaccctgc tgtagcanga ataaagaagc aagggattaa cacttaaaaa      240
aacngccaaa ttcctgaacc aaatcattgg catttttaaa aagggataaa aaaacnggnt      300
aaggggggga gcattttaag taaagaangg ccaaggggtg tatgccngga c                351

```

<210> 88

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 88

```

gttttaggtc tttaccaatt tgattggttt atcaacaggg catgaggttt aaatatatct      60
ttgaggaaag gtaaagtcaa atttgacttc ataggtcacg ggcgtcctca ctctgtgca      120
ttttctggtg gaagcacaca gttaattaac tcaagtgtgg cgntagcgat gctttttcat      180
ggngtcattt atccacttgg tgaacttgca cacttgaatg naaactcctg ggtcattggg      240
ntggccgcaa gggaaagggt cccaagacac caaaccttgc aggggtacctn tgcacaccaa      300
c                                                                    301

```

<210> 89

<211> 591

<212> DNA

<213> Homo sapien

<400> 89

```

tttttttttt tttttttatt aatcaaatga ttcaaaacaa ccatcattct gtcaatgccc      60
aagcaccag ctggctctct ccccatatgt cacactctcc tcagcctctc cccaaccct      120
gctctccctc ctcccctgcc ctagcccagg gacagagtct aggaggagcc tggggcagag      180

```

ctggaggcag	gaagagagca	ctggacagac	agctatgggt	tggattgggg	aagagattag	240
gaagtaggtt	cttaagacc	cttttttagt	accagatata	cagccatatt	cccagctcca	300
ttattcaaat	catttcccat	agcccagctc	ctctctgttc	tccccctact	accaattctt	360
tggctcttac	acaattttta	tccctcaaat	attcatccct	ggcccaacca	gtccccctgag	420
cctccctctg	gtggagactc	ctccacccat	gagctcccca	gagcatccaa	gacagagtgc	480
acagagacct	ggggaaggaa	gctgaacttt	gcagagatgt	ggacagggtgc	aggctagggt	540
acagggtggt	ggtagaggag	acaagtttta	tttccaggcc	cacagtctct	c	591

&lt;210&gt; 90

&lt;211&gt; 1978

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 90

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&lt;210&gt; 91

&lt;211&gt; 895

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 91

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&lt;210&gt; 92

&lt;211&gt; 1692

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 92

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&lt;210&gt; 93

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 93

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&lt;210&gt; 94

&lt;211&gt; 735

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 94

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&lt;210&gt; 95

&lt;211&gt; 578

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 95

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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	540
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa			578

&lt;210&gt; 96

&lt;211&gt; 594

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 96

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&lt;210&gt; 97

&lt;211&gt; 3101

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 97

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&lt;210&gt; 98

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 98

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Val Ser Ala Gln Asn Pro Thr Thr Ala Ala Pro Ala Asp Thr Tyr Pro
 20          25          30
Ala Thr Gly Pro Ala Asp Asp Glu Ala Pro Asp Ala Glu Thr Thr Ala
 35          40          45
Ala Ala Thr Thr Ala Thr Thr Ala Ala Pro Thr Thr Ala Thr Thr Ala
 50          55          60
Ala Ser Thr Thr Ala Arg Lys Asp Ile Pro Val Leu Pro Lys Trp Val
 65          70          75          80
Gly Asp Leu Pro Asn Gly Arg Val Cys Pro
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&lt;210&gt; 99

&lt;211&gt; 197

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 99

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Met Ala Lys Asn Gly Leu Val Ile Cys Ile Leu Val Ile Thr Leu Leu
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 20          25          30
Ser Lys Arg Arg Val Arg Asp Lys Asp Gly Asp Leu Lys Thr Gln Ile
 35          40          45
Glu Lys Leu Trp Thr Glu Val Asn Ala Leu Lys Glu Ile Gln Ala Leu
 50          55          60
Gln Thr Val Cys Leu Arg Gly Thr Lys Val His Lys Lys Cys Tyr Leu
 65          70          75          80
Ala Ser Glu Gly Leu Lys His Phe His Glu Ala Asn Glu Asp Cys Ile
          85          90          95
Ser Lys Gly Gly Ile Leu Val Ile Pro Arg Asn Ser Asp Glu Ile Asn
          100          105          110
Ala Leu Gln Asp Tyr Gly Lys Arg Ser Leu Pro Gly Val Asn Asp Phe
          115          120          125
Trp Leu Gly Ile Asn Asp Met Val Thr Glu Gly Lys Phe Val Asp Val
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                                          180                                      185                                      190  
 Phe Thr Ile Pro Gln  
                                          195

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 <211> 3410  
 <212> DNA  
 <213> Homo sapien

<400> 100  
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&lt;210&gt; 101

&lt;211&gt; 553

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 101

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35     40     45
Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly
50     55     60
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65     70     75     80
Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile
85     90     95
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Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr
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 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu  
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 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala  
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 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly  
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 Lys Ser Asp Leu Ala Lys Tyr Ser Ala  
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&lt;211&gt; 940

&lt;212&gt; DNA

&lt;213&gt; Human

&lt;400&gt; 102

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